Lung cancer and non-malignant lung diseases among Norwegian silicon carbide industry workers – associations with particulate exposure factors.

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1 Contents

2 Summary in English

The main theme of this thesis was to examine the risk of lung diseases among Norwegian silicon carbide workers, and how these diseases relate to different occupational exposure factors. The background for this was previously observed high incidences of pneumoconiosis, lung cancer, and obstructive lung diseases among workers in Norwegian silicon carbide plants. In addition, other cancer sites and other causes of death have also been examined.

Two epidemiological approaches have been applied; 1) a historical prospective study of cancer incidence and mortality in a cohort of all male workers employed in the Norwegian silicon carbide industry from start of production in 1913 to 2003, and still alive in 1951/1953, when the Norwegian Cause of Death Registry and the Cancer Registry of Norway, respectively, were established, and 2) a longitudinal study over five years (1997-2003) of changes in lung function among current workers in the industry.

In the first study, lung cancer incidence and mortality from obstructive lung diseases were analyzed in relation to cumulative exposures to total dust, respirable dust, respirable quartz, cristobalite, and silicon carbide, and silicon carbide fibers. The estimated dust levels were based on a recently developed historical job exposure matrix (JEM), based on more than 8000 measurements. In addition, time related factors like period of first employment, duration of employment, and time since first employment were included in the analyses together with confounding factors such as age, period of diagnosis, and smoking. In the second study, the annual decline in lung function during a 5-year period was related to estimated levels of total dust, based on a period specific JEM.

Both lung cancer incidence and mortality from obstructive lung diseases were increased compared to the general population. The lung cancer incidence was highest among the workers with short employment duration (< 3 years), but was also high among those who had worked more than 20 years in the industry. We found an association between lung cancer incidence and work in the furnace hall, where especially exposure to cristobalite and possibly silicon carbide fibers seemed to be the most important causal factors. Mortality from obstructive lung diseases was also increased among the long-term workers (> 3 years of employment). Here, we found associations with work in highly dust exposed areas, both furnace and processing department. Exposure-response associations were found with total dust and silicon carbide dust, and a weaker association was found with cristobalite exposures of long duration (> 15 years). Among the more recently employed workers, we found that total dust exposure was associated with an increased annual reduction of lung function during a five-year period, both among smokers and non-smokers.

3 Norsk sammendrag

Avhandlingens hovedtema er forekomst av lungesykdommer blant arbeidere i norsk silisiumkarbidindustri, og hvordan disse sykdommene kan være knyttet til ulike eksponeringsfaktorer i yrket. Bakgrunnen for prosjektet er at man tidligere har observert høy forekomst av støvlungesykdom (pneumokoniose), lungekreft og obstruktive lungesykdommer blant silisiumkarbidindustriarbeidere. Forekomst av andre kreftformer og dødsårsaker er også blitt undersøkt.

To epidemiologiske studier er gjennomført; 1) en undersøkelse av kreft og dødelighet i en kohort av alle mannlige arbeidere ansatt i den norske silisiumkarbidindustri fra produksjonen startet i Norge i 1913 frem til 2003, og som fremdeles var i live i 1951/1953, da henholdsvis det norske Dødsårsaksregisteret og Kreftregisteret ble etablert, og 2) en longitudinell studie over fem år (1997-2003) om endringer i lungefunksjon blant nåværende arbeidere i industrien.

I studie 1) er forekomst av lungekreft og dødelighet av obstruktive lungesykdommer analysert i relasjon til kumulativ eksponering for totalstøv, respirabelt støv, respirabel kvarts, kristobalitt og silisiumkarbid, og silisiumkarbidfiber. De estimerte støvnivåene var hentet fra en nylig utviklet historisk jobbeksponeringsmatrise (JEM) basert på mer enn 8000 støvmålinger. I tillegg ble tidsrelaterte faktorer, som periode for første ansettelse, ansettelsesvarighet og tid siden første ansettelse, studert i analysene sammen med konfunderende faktorer som alder, periode for diagnose og røyking. I studie 2) ble årlig reduksjon av lungefunksjon gjennom en femårsperiode relatert til estimerte totalstøvsnivåer, basert på en JEM for den aktuelle perioden.

Både lungekreftforekomst og dødelighet av obstruktive lungesykdommer var høyere enn i den generelle befolkningen. Lungekreftforekomsten var høyest blant arbeidere med kort ansettelsesvarighet (< 3 år), men var også høy blant dem som hadde jobbet mer enn 20 år i industrien. Vi fant en sammenheng mellom økt forekomst av lungekreft og arbeid i ovnshall, hvor spesielt eksponering for kristobalitt og muligens silisiumkarbidfibre syntes å være de viktigste årsaksfaktorene. Dødelighet av obstruktiv lungesykdom var også økt blant de langtidsansatte (> 3 år). Her fant vi assosiasjoner mellom arbeid i svært støvutsatte områder, både i ovn og prosessavdeling, og dødelighet av obstruktive lungesykdommer. Vi fant assosiasjoner med eksponering for totalstøv og silisiumkarbidstøv, og en svakere sammenheng ble funnet med kristobalitteksponering av lang varighet (> 15 år). Blant de mer nylig ansatte fant vi at totalstøveksponering var assosiert med en økt årlig reduksjon av lungefunksjonen over en femårsperiode, både blant røykere og ikke-røykere.

4 Acknowledgements

The research work which is the basis for this thesis is performed at the National Institute of Occupational Health in the period 2003-2011. On completing the work, I will express my deepest thanks to all the people who have contributed in many ways during all these years.

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Solveig Føreland has been my co-research fellow during the whole project; she has performed the exposure measurements and developed the job exposure matrix. Thank you for your incredible effort to make the outcome of this study possible, and thank you for interesting discussions and excursions along the way.

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plants, and I have always been met with a positive attitude and willingness to help. A special thanks to Irene Espenes, Åse Sjøgård Sæterbakk and Trond Klemetsen. At the start of the project, I also received a lot of help from the personal administrations at the plants with updating of the cohort. Thank you.

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5 List of publications

This thesis is based on the following four publications, which will be referred to in the text by their Roman numerals:

- **Paper I**: Bugge MD., Kjuus H., Martinsen JI., Kjærheim K. Cancer incidence among short- and long-term workers in the Norwegian silicon carbide industry. Scand J Work Environ Health 2010;36(1):71-9.

- **Paper II**: Bugge MD., Føreland S., Kjærheim K., Eduard W., Martinsen JI., Kjuus H. Mortality from non-malignant respiratory diseases among workers in the Norwegian silicon carbide industry: associations with dust exposure. Occup Environ Med 2011;68:863-9 doi:10.1136/oem.2010.062836.

- **Paper III**: Bugge MD., Kjærheim K., Eduard W., Føreland S., Kjuus H. Lung cancer incidence among Norwegian silicon carbide workers – associations with particulate exposure factors. Submitted Occup Environ Med.

- **Paper IV**: Johnsen HL., Bugge MD., Føreland S., Kjuus H., Kongerud J., Søyseth V. Dust exposure is associated with accelerated lung function loss among workers in the Norwegian silicon carbide industry. Submitted Scand J Work Environ Health.

6 Abbreviations

AIC:	Akaikes information criterion
AM:	Arithmetic mean
CI:	Confidence interval
CO:	Carbon monoxide
ECCS:	European Community for Coal and Steel
FEV_1:	Forced expiratory volume in the first second
FVC:	Forced vital capacity
GM:	Geometric mean
GSD:	Geometric standard deviation
h^2:	Squared height
IARC:	International Agency for Research on Cancer
ICD:	International classification of diseases
IRR:	Incidence rate ratio
JEM:	Job exposure matrix
JOEH:	Journal of Occupational and Environmental Hygiene
LMM:	Linear mixed models
LOD:	Limit of detection
LR-test:	Likelihood ratio test
NIOH:	National Institute of Occupational Health
OCP:	Oral cavity and pharynx
OEL:	Occupational exposure limit
OLD:	Obstructive lung diseases: Asthma, chronic bronchitis, emphysema, and chronic obstructive pulmonary disease
OSHA:	Occupational Safety and Health Administration (USA)
PAH:	Polycyclic aromatic hydrocarbons
$r_{Pearson}$:	Pearson's correlation coefficient
SiC:	Silicon carbide
SiCwh:	Silicon carbide whiskers
SIR:	Standardized incidence ratio
SMR:	Standardized mortality ratio
SO_2:	Sulfur dioxide

7 Background

7.1 History of silicon carbide production in Norway

Edward Goodrich Acheson patented in 1893 a method for producing carborundum (silicon carbide) powder, which later was named the Acheson method. The primary appliance of the material was as an abrasive, as silicon carbide (SiC) has hardness close to that of diamond. When the Norwegian founder Sam Eyde was planning an industry establishment at the outskirts of Arendal in the southern Norway, he chose to start up production of abrasives, at first both corundum (aluminium oxide) and carborundum, but from 1928 only SiC was produced at the plant. From 1920-1960 the production increased gradually, with exception of the years 1943-1946, when the factory was closed due to a sabotage action during the World War 2. In 1963 the second Norwegian SiC plant started production in Orkanger, in the middle part of Norway, and in 1965 the third plant started up, in Lillesand, 50 kilometers from the first plant in Arendal. In the later years, some of the raw material production has moved to other countries, and a larger part of the activity at the Norwegian plants is concentrated on the high technology processing of the raw material into end products.

Photo 1: Saint-Gobain Ceramic Materials AS, Arendal, the first SiC plant in Norway.

7.2 Epidemiological studies on health effects related to silicon carbide production

7.2.1 Non-malignant respiratory effects

Only a few epidemiologic studies are previously performed in the SiC industry. In addition, a few case studies and reports are published. In 1929 Winslow, Greenburg and Greenberg documented a high prevalence of tuberculosis among SiC industry workers. They drew attention to the hard and sharp dust particles in the working atmosphere, and postulated that "We have every reason to expect ... that dusts of this nature should be exceedingly deleterious to health" (Winslow et al., 1919). During the 1930ies, a concern about silicosis risk arose in the Norwegian smelting industries. Arne Bruusgaard, who was a physician in the Norwegian Labour Inspectorate, presented in 1948 results from an x-ray surveillance study in the Norwegian SiC industry on a London congress. He found that among 222 examined SiC workers, 49 had silicosis. What was of special concern in his study was that he found that 37 of these workers with silicosis had most unlikely worked with crystalline silica, but with the finished product, SiC, only (Bruusgaard, 1948). In a study of Marcer et al., profusion of parenchymal opacities was associated with cumulative dust exposure in the SiC industry, and reduced FEV_1 (forced expiratory volume in the first second) was associated with cumulative exposure, profusion of opacities, and smoking (Marcer et al., 1992). Osterman et al. published two papers in 1989, showing that SiC production workers had increasing symptoms of phlegm, wheeze, and cough, related to increasing levels of exposure to sulfur dioxide (SO_2) (Osterman et al., 1989a); and significant decrements of FEV_1 and forced vital capacity (FVC) related to each year of employment (Osterman et al., 1989b). Bronchial hyper-reactivity was found in 19 out of 50 SiC-workers with respiratory symptoms (Petran et al., 2000), and workers in the SiC production line had a steeper annual fall in FEV_1 in a 5 year follow-up, than the non-line-workers (Soyseth et al., 2007). A mortality study in the Norwegian SiC industry showed increased mortality from asthma, emphysema and chronic bronchitis (SMR 2.2, 95% CI 1.6-3.0). An association with increasing total dust levels were shown (Romundstad et al., 2002).

7.2.2 Lung cancer

In 1994 came the first cohort mortality study published from the SiC industry, by Infante-Rivard et al, showing that the SiC workers had an increased mortality from lung cancer

(SMR 1.7, 95% CI 1.1-2.5) and non-malignant respiratory diseases (SMR 2.0, 95% CI 1.2-3.2). There were also shown exposure-response associations with total dust exposure. The study, however was quite small (N=585), and further studies were recommended (Infante-Rivard et al., 1994). A Norwegian cancer incidence study from 2001 showed a standardized incidence ratio (SIR) for cancer, all sites, of 1.2 (95% CI 1.1-1.3), and for lung cancer 1.9 (95% CI 1.5-2.3). Lung cancer risk increased according to cumulative exposure to total dust, SiC fibers, SiC particles and crystalline silica. The risk of lung cancer was 3-4 times increased at the highest level of fiber exposure relative to the non-exposed (Romundstad et al., 2001).

Photo 2: Washington Mills AS, Orkanger.

7.3 Project background

The results of two studies performed by the Cancer Registry of Norway from 2001/2002 (Romundstad et al., 2001, 2002) gave rise to concern, both among employers and employees in the SiC industry, and among other stakeholders, including labour authorities and politicians. A question was raised if it was possible to further identify specific exposure factors that could be responsible for the increased risk of lung cancer and mortality from non-malignant lung diseases among the workers. In the two studies the exposure assessment was based mainly on historical measurements of total dust exposure, with only a few

measurements of other exposure factors. It was therefore decided to do a new follow-up study among the SiC workers, with revised and more detailed exposure assessment. Thus, a large exposure assessment study was initiated which should provide more detailed information about each job groups' relative exposures to several exposure factors. This should give a basis for construction of a comprehensive historical job exposure matrix, for use in the present renewed epidemiological studies on cancer incidence and mortality among workers in the Norwegian SiC industry.

Photo 3: Saint-Gobain Ceramic Materials AS, Lillesand.

8 Aims of the study

The main aim of the study was to examine the role of specific occupational exposure factors related to the risk of lung cancer and obstructive lung diseases (OLD) among Norwegian SiC industry workers.

In particular

- To examine lung cancer incidence and OLD mortality in an updated cohort of Norwegian SiC industry workers
- To investigate the association between cumulative exposure to quartz, cristobalite, SiC particles, and SiC fibers, and lung cancer incidence
- To investigate the association between cumulative exposure to quartz, cristobalite, SiC particles, and SiC fibers, and OLD mortality
- To examine the role of time-related factors, such as duration and period of employment, and latency time, with respect to lung cancer incidence and OLD mortality among workers in the Norwegian SiC industry
- To study the association between dust exposure and annual changes in lung function among Norwegian SiC industry workers

An additional aim was to study the incidence of cancer at other sites, and mortality from other causes among workers in the Norwegian SiC industry.

9 About the silicon carbide industry

9.1 Silicon carbide

SiC (Chemical composition Si-C) is an industrially produced material. SiC in natural form (moissanite) is very rare, and is only incidentally found. SiC is an extremely hard material; 9.5-9.75 on the Mohs Scale of Hardness, next only to diamond, cubic boron nitride, and boron carbide in hardness (Liethschmidt, 1993), and was originally produced for the application as an abrasive. Subsequent studies have shown that SiC is heat and chemical resistant, and has semiconducting properties. The diversity of its uses has increased accordingly, among others; to refractory and ceramic materials, electrical resistors, light-emitting diodes, diesel particle filters, and wire-saws for solar cell production.

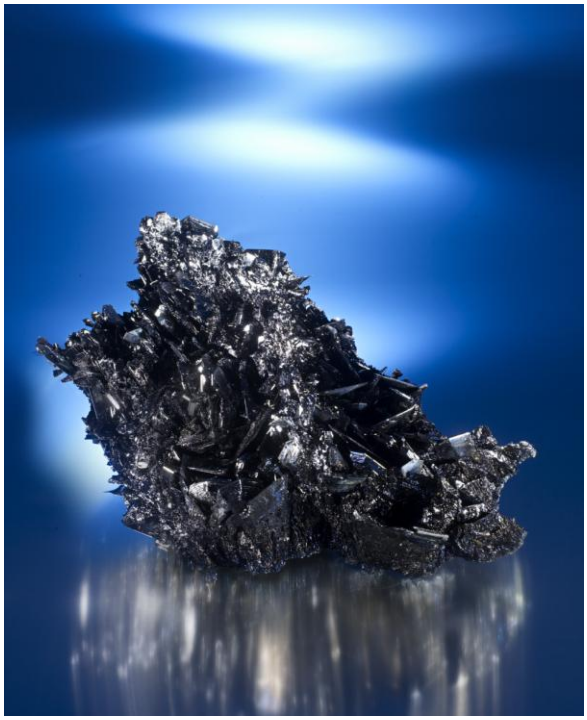

Photo 4: SiC.
Courtesy: Washington Mills

9.2 Silicon carbide production process

By the Acheson method, a mixture of finely ground quartz sand and petroleum coke, often with additives like sawdust, salt and other minerals, are placed in open furnaces with removable concrete side walls, and electrodes at each end. A graphite core in the middle of

the mix functions as an electric leader. The burning process lasts about 48 hours, during which the temperature can reach about 2500˚C close to the core. Via a gas phase reaction at a temperature > 1700˚C the silicon in the quartz and the carbon in the coke combine and form SiC and carbon monoxide (CO), according to the overall equation:

$SiO_2 + 3\,C \longrightarrow SiC + 2\,CO.$

At the end of the burning process, the zone closest to the core consists of a thick layer of loosely knitted SiC crystals, whereas the periphery consists of unreacted material. The zone between those two layers consists of partially reacted material.

The furnaces are allowed to cool for several days before the side walls are removed. In the furnace halls, 4-6 furnaces form a group associated to a single transformer, with one furnace always in operation while the others are in different stages of recharging, cooling or being broken down (Liethschmidt, 1993).

Photo 5: Furnaces in different stages of production.
Courtesy: Saint-Gobain.

The unreacted and partially reacted material is removed before further processing, and is reused as raw material in new furnace cycles. The refinery process includes several crushing and sieving procedures, chemical treatment, and classification into different grain

sizes and qualities, according to desired end use. A detailed description of the production process is published by Solveig Føreland et al. (Føreland et al., 2008).

Photo 6: SiC in the furnace hall, before processing.
Courtesy: Saint-Gobain.

The workers in the SiC production industry are exposed to a large variety of airborne particulates and gases; the diversity being greatest in the furnace hall. The raw materials consist of quartz and petrol coke, in addition to unreacted and partly reacted material from previous furnace cycles. Graphite is used as electric leader, and some graphite is also formed during the heating process. During the heating process some of the quartz is converted to cristobalite, giving a higher concentration of cristobalite than quartz in some of the working processes (Føreland et al., 2008). SiC fibers are formed during the heating process (Bye et al., 1985), and these are most frequently found in the borderline zone between partly reacted and fully reacted SiC (Gunnæs et al., 2005). Polycyclic aromatic hydrocarbons (PAH) are to a certain degree liberated from the petrol coke during heating, and SO_2 is also formed, depending on the sulfur content of the coke. CO is an important product of the furnace heating process, and represents a life threatening danger which is controlled to a certain degree by igniting the gas at the furnace surface. Nowadays, a constant personal monitoring of the CO levels in the furnace hall is performed. The end

product of the heating process is non-fibrous SiC, and this also represents an important part of the mixed airborne exposure in the furnace hall (20-40% of the respirable dust).

In the processing department non-fibrous SiC is the far most important exposure, and represents 60-80% of the respirable dust. In addition, some remnants from the furnace hall, mainly crystalline silica, are found in the processing department, but these are cleared out during the refining of the product, giving a more and more clean SiC exposure towards the end of the process.

Maintenance personnel; electricians and mechanics, work all over the plant, and are exposed to dust from all departments, in periods at very high levels, but with a shorter duration than workers affiliated to the respective departments, giving an all over lower exposure.

Photo 7: Furnace with burning CO-gas.
Courtesy: Washington Mills

10 Specific exposure factors and their health effects

10.1 Crystalline silica: Quartz and cristobalite

Most literature on health effects of crystalline silica have no information on which type of crystalline silica is considered. As quartz is the most abundant crystalline silica polymorph occurring in nature, it is reason to believe that when only the term "crystalline silica" is mentioned in a paper, quartz is the exposure factor of concern.

Quartz is studied extensively in toxicological studies, and cytotoxic (Fanizza et al., 2007; Li et al., 2007) and carcinogenic (Johnson et al., 1987; Spiethoff et al., 1992) effects are documented. Comparisons between different quartz specimens, however, have shown very differing biological responses (Bruch et al., 2004; Seiler et al., 2004). Freshly crushed quartz is shown to be more biologically active than aged quartz (Vallyathan et al., 1995). Some theories suggest that surface properties of the quartz may be an important factor (Donaldson and Borm, 1998; Fubini, 1997), and also that the biological effect of quartz may be modified by other substances, some of which originate from other minerals (Donaldson and Borm, 1998; Engelbrecht and Thiart, 1972). Comparisons between quartz and cristobalite concerning fibrogenic (King et al., 1953; Zaidi et al., 1956) and inflammatory (Hemenway et al., 1986) effects have consistently shown that cristobalite is more biologically active than quartz. Cristobalite is shown to be more carcinogenic than quartz, and the clearance of cristobalite from the lungs is slower than that of quartz (Hemenway et al., 1990).

IARC (International Agency for Research on Cancer) classified crystalline silica as a Group 1 carcinogen (carcinogenic to humans) in 1997 (IARC, 1997), a decision which has recently been confirmed (IARC, 2011), after consideration of a new pooled analysis (Steenland et al., 2001) and several meta-analyses adding weight to the evidence. Several papers have been published with criticism of the IARC decision, where it is argued that even though animal experiments show a carcinogenic effect from crystalline silica, the evidence from epidemiological studies is too conflicting to conclude definitely about the effect on humans. The fact that quartz is one of the most abundant minerals in the earth's crust, and that many companies are dependent on this raw material, naturally adds to the temperature in the discussion (Gamble, 2011). It has been suggested that the carcinogenic effect of crystalline silica is due to the effects of cristobalite only (McDonald and Cherry,

1999), as several of the epidemiological studies showing a positive exposure-response association with lung cancer are from industries where cristobalite are formed in a heating process (Checkoway et al., 1999; Cherry et al., 1998). However, also evidence from industries with possible cristobalite exposure is sparse; a study in the pottery industry showed an association of lung cancer with intensity of silica exposure, but not with cumulative exposure (Cherry et al., 1998); in the Californian diatomaceous earth industry an exposure response association with cumulative crystalline silica exposure was shown (Checkoway et al., 1997; Rice et al., 2001); and a cohort study from the Italian refractory brick industry showed an excess of lung cancer, increasing with duration of employment and time since first employment (Merlo et al., 1991).

The association between exposure to crystalline silica and silicosis is less conflicting, (Graham, 1998), and although this serious disease is not common in the Norwegian SiC industry nowadays, the concern about deleterious health effects from the working environment arose primarily because of silicosis. In addition, epidemiological evidence for an association between occupational exposure to crystalline silica dust and chronic obstructive pulmonary disease, independent of silicosis, has been presented (Hnizdo and Vallyathan, 2003).

10.2 Silicon carbide fibers

Most of the toxicological research on fibrous SiC is performed on silicon carbide whiskers (SiCwh), which are industrially produced, and are used as reinforcement material in ceramics and metals. Comparisons have been made between the fibers formed in the Acheson process and SiCwh, concluding that the fiber types show many similarities (Skogstad et al., 2006). We therefore presume that the results from the toxicological studies of SiCwh are relevant for the fibers represented in exposures in the SiC industry.

The studies of asbestos and other fibers showed that important factors determining the toxicological effects of fibers were dimension (long and thin particle (Lipkin, 1980; Miller et al., 1999a; Miller et al., 1999b; Stanton et al., 1981)), and biopersistence (Miller et al., 1999b). SiC fibers have a high biopersistence (Akiyama et al., 2007; Searl et al., 1999), and fulfill the dimension criteria defined by Stanton et al. (Skogstad et al., 2006; Stanton et al., 1981). Comparisons between SiCwh and other fibers and particles showed that SiCwh had effects similar to asbestos, both with regard to carcinogenicity (Lipkin, 1980; Miller et

al., 1999b; Stanton et al., 1981), and cytotoxicity (Birchall et al., 1988; Vaughan et al., 1991a). Cigarette smoke seemed to enhance the uptake of SiCwh in tracheal epithelium (Keeling et al., 1993), giving cell destruction, cell death (Vaughan et al., 1991b) and subepithelial necrotic foci (Vaughan et al., 1991b). SiCwh was also shown to give mesothelioma (Johnson and Hahn, 1996; Miller et al., 1999b; Vasil'eva et al., 1989) and pneumoconiotic nodules (Begin et al., 1989).

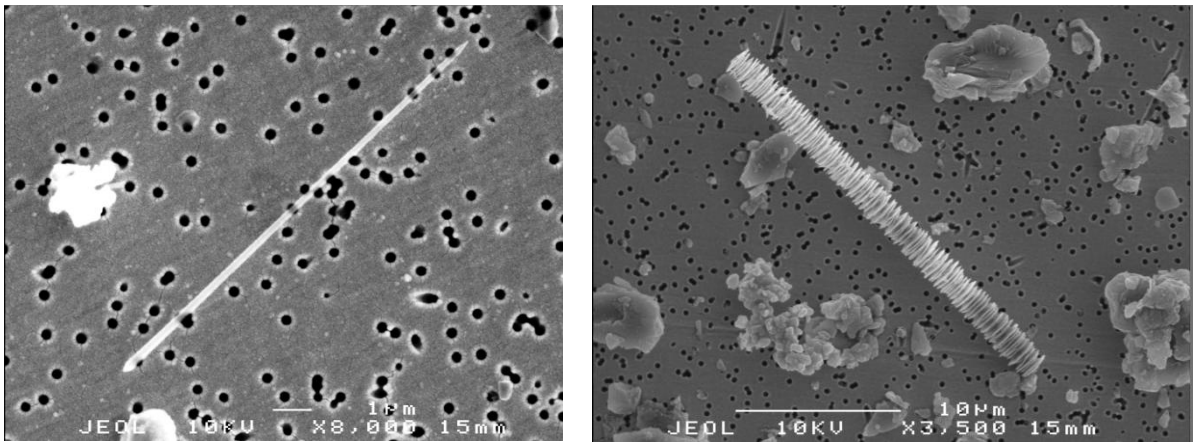

Photo 8: SiC fibers, photographed through a scanning electron microscope.
Courtesy: Asbjørn Skogstad, NIOH

Thus, the toxicological studies suggest that SiC fibers may represent a considerable hazard to the health of exposed workers, with risk of lung cancer, mesothelioma, pneumoconiosis and possibly other inflammatory diseases of the lung.

Only a few studies of workers are published where exposure to SiC fibers are specifically mentioned. Previous SiC industry workers who died of pneumoconiosis or lung cancer had a high level of fibers in the lung parenchyma at autopsy (Dufresne et al., 1995; Dufresne et al., 1993). Romundstad et al. showed an exposure-response association between SiC fiber exposure in the Norwegian SiC industry and lung cancer incidence (Romundstad et al., 2001). Other epidemiologic studies in the SiC industry have not presented estimates of fiber exposure.

10.3 Silicon carbide particles

In an early toxicological study of SiC, Gardner studied the effect of massive SiC inhalation exposure on healthy and tuberculous guinea pigs. Pigmented dust deposition was found all over the lungs, but this did not seem to affect the healthy animals. The tuberculous animals,

however, got a more severe disease, and dust deposits were found in and around tubercles in the lungs. There was also an increased tendency for reinfection with following progressive pulmonary tuberculosis (Gardner, 1923). Silicosis from quartz exposure was increased with parallel exposure to SiC, whereas the SiC exposure did not worsen asbestosis (Engelbrecht and Thiart, 1972). Several later toxicological studies have examined the carcinogenicity and cytotoxicity of SiC particles, without any positive results (Bruch et al., 1993a; Bruch et al., 1993b; Rehn et al., 1992). Based on these studies, it was assumed that SiC particles were practically "inert", i.e. that it produced no tissue damage (Bruch et al., 1993b).

The toxicological studies give no indications of carcinogenic or fibrogenic potential of SiC particles. It is possible that the material can give inflammatory reactions and enhance toxic effects of other substances.

An interesting observation from the Bruusgaard study in 1948 (Bruusgaard, 1948), was that among 32 workers who were believed to be exposed to SiC dust only (not crystalline silica), ten workers had clear pneumoconiotic changes on the x-ray. Some of these had also silicosis grade 2 or 3, and some invalidity was also seen (Bruusgaard, 1948). More recent epidemiologic studies have been performed in the abrasive and grinding industry, where SiC dust was part of a mixed exposure. Some of these studies showed an increased incidence of respiratory disease (Cukier et al., 1991; Ruttner et al., 1987), others did not (Edling et al., 1987). The mixed dust exposure both in the SiC producing industry and in the abrasive industries make findings difficult to interpret with relation to the isolated effect of SiC.

10.4 Other exposures in the SiC industry

Exposure to PAHs in the SiC furnace hall has previously been reported (Dufresne et al., 1987; Petry et al., 1994; Smith et al., 1984). Exposures to some PAHs are classified as carcinogenic to humans by IARC (IARC, 2010), and in some industries an excess of lung cancer is associated with PAH exposure (IARC, 2010). Previous measurements in the SiC industry have, however, shown low levels of PAH exposure, with the only exception measurements from crane workers working in open windowed crane cabins (Smith et al., 1984).

Exposure to SO_2 gas has been associated with respiratory effects such as bronchoconstriction (Johns and Linn, 2011). Depending on the sulfur content of the coke, SO_2 can be emitted to the working environment in the SiC furnace halls.

CO gas is a well known health risk in the SiC industry, primarily associated with sudden death because of poisoning, but CO gas is also associated with effects on the cardiovascular system (Kristensen, 1989; Zenz, 1979).

Asbestos is known as a cause of pneumoconiosis (asbestosis), lung cancer and mesothelioma. The material has been used in the SiC industry as isolating material in the furnaces, and during our project work we have heard histories told by experienced workers about the mechanics and "furnace builders" sawing asbestos plates inside the furnace hall.

11 Materials and methods

11.1 Study population

11.1.1 Cancer/mortality cohort

11.1.1.1 History of the cohort

The Cancer Registry of Norway performed a cancer incidence study in the Norwegian SiC plants in the 1980-ies. A database was established on the basis of personnel registers in the plants, with names, dates of birth, ID-number, and employment information: start and end of each employment period, department and type of job. Only men were included. The personnel registers in the oldest plant were the least complete. Here, the oldest protocol (1913-1928) of employees included only names, dates of birth and dates of first employment. End of employment was not registered for all employees. A later protocol (1928-1952) included in most cases department affiliation, but also here end date was missing for some persons. Because of the silicosis concern in the early 1940-ies a full record of previous employment in the SiC industry was established for all current employees in 1942, and from this year a personal card was kept on each employee, which was updated each week with job information. From 1948 a medical card was kept in addition. These protocols and cards were used in establishing the study cohort. By comparing the different sources, quite a few employment records could be followed all back to the start of the plant, in 1913. The database included 1537 men with employment duration of one year or more in the period 1913-1974. The follow-up of cancer incidence was from 1953 (start of the Cancer Registry of Norway) to 1986, and an increased incidence of lung, lip, and stomach cancer was documented (Andersen and Høy: Report on cancer incidence and cause specific mortality at silicon carbide plants, Smelteverksindustriens Helseutvalg (SIHU) dok. 77, May 1988, in Norwegian). The increased incidence of lung cancer was only seen among persons with less than 4 years employment duration.

These findings gave the incentive for an extended study. Additional persons were added to the original cohort, and employment data was extended until 1996. Now, a total of 2720 men with employment duration of 6 months or more were included in the database. 40 of these men had died before start of follow-up in 1953, and 60 persons were not traceable in the Statistics Norway. Accordingly, 2620 men were included in a new follow-up of

cancer, from 1953-1996 (Romundstad et al., 2001). A mortality study was also performed on the basis of the same cohort. Here, follow-up was limited to the period 1962-1996 due to the digitalization limitations in the Cause of Death Registry, and 2562 men were included (Romundstad et al., 2002). From 2003, a new revision of the cohort was performed with the aim of updating both the cancer- and the mortality study. Employment dates and job codes were updated until the end of 2003, and new workers employed after 1996 (N=130) were added to the cohort. One double registration from the previous database was deleted, and three persons previously not traced were added to the database. Altogether, 2752 persons with at least 6 months employment duration, and alive after 1953, were registered. In addition, for the mortality study, 6 persons who died between 1951 and 1953 were added to the cohort, as the Cause of Death Registry was established in 1951, and access had become digitally available also to the causes of death before 1962. Before we could update the cancer diagnoses the Norwegian Data Inspectorate claimed that all registered persons who were still living should be informed about the study, and given the opportunity to refuse participation. The information was sent out to 1519 persons, and 121 refused participation in the study, leaving us with a cohort including 2637 previous and current workers with at least 6 months' sum of employment, and alive 1 January 1951 or later.

The information registered was name, date of birth, the Norwegian unique ID-number (established in 1964, and given to all Norwegians alive in 1960 or born later), smoking habits, and dates of start and end, and job codes, for all employment periods in the SiC industry. Information about smoking was collected from the workers' medical cards at the plant occupational health services. This information was usually only registered once in the medical card, and seldom updated, and as a result the information recorded in the database and applicable in the study was "smoker", "non-smoker", "quitted", or "not registered". As this information was registered only once, and no date of registering was available, the "quitted" category became meaningless in the follow-up study. We therefore decided on three categories: "Ever-smoker", "never-smoker" and "unknown". The ever-smokers were a large majority, about 70% of the workers.

11.1.1.2 Sub-sections of the cohort were used in the three following studies:

Paper I included the sub-cohort alive after 1953, 2631 workers, divided in 944 short-term workers (< 3 years sum of employment) and 1687 long-term workers. We wanted to exclude the short-term workers quitting because of disease or death, and decided to start the follow-up of this group one year after end of employment. This excluded 19 men who either

emigrated or died during this year. The study therefore included 2612 men; 925 short-term workers and 1687 long-term workers. Start of follow-up for the long-term workers, was after 3 years of total employment.

Paper II included the whole cohort of 2637 workers alive 1951 or later. After linkage with the Cause of Death Registry, we found that 8 persons with a date of death in the National Statistics did not have a death diagnosis in the Cause of Death Registry. These persons were excluded from the study. Because of the results from Paper I, where short-term workers showed a high risk of several cancers which we did not believe was due to work in the SiC industry, we chose to perform the exposure related analyses on long-term workers only. This left 1687 long-term workers for the follow-up.

Paper III included the 2631 workers alive after 1953. For the same reason as in Paper II we chose to perform the exposure related analyses on long-term workers only. 1687 men fulfilled this inclusion criterion also in this study.

11.1.2 OLD cohort

The study group in Paper IV was assembled in a different way. The study was part of a survey in all Norwegian smelters which were members of the Federation of Norwegian Industries. All persons, both men and women, office and production workers, which were employed in the SiC industry in the study period 1997-2003, and aged 20-55 years by inclusion, were invited to participate in an annual lung function test, and answer a questionnaire. 456 workers in the three plants (80-90 % of the employees at the time of inclusion) participated at one or more (up to 5) examinations.

11.2 Exposure assessment and job exposure matrix

11.2.1 Historical exposure data

When the silicosis risk in the SiC industry was acknowledged in the 1940ies, the only Norwegian SiC plant existing at that time started regular measurements of dust exposures. At the start, the method used was particle counting, later (in the 1960ies) gravimetrical measurements were performed. In the two other plants dust measurements were performed from start of production in the 1960ies. These regular measurements were mainly total dust samples performed in connection to tasks known to be associated with high exposure. A few measurements were done of crystalline silica exposure, and some fiber countings were also

performed. In addition, exposure assessment studies were performed during projects organized by the Norwegian Institute of Occupational Health (NIOH), the first of these studies taking place in 1975. In 1985 the results from a large exposure assessment study was published, where the contents of the furnace hall air was studied in detail. This was the first time SiC fibers were discovered in the furnace hall atmosphere (Bye et al., 1985). A large number of total dust measurements were thus available at the start of the present project, but only a few measurements of specific factors. Additional information about changes in work organization, working hours, and technical improvements, was collected through interviews with experienced workers, and was supplemented with information from written reports.

11.2.2 Comparative exposure assessment study

A basic idea in the present project was that although the total dust levels were decreased during the years due to technical improvements and changes in the organizing of the work, the composition of the dust, i.e. the fractions of the specific dust factors in the dust associated with each job, was supposed not to have changed. A comprehensive comparative exposure assessment study was therefore initiated. During 2002-2003 about 6-700 measurements of total dust were collected in parallel with measurements of fibers and respirable dust. Fibers were counted using light microscopy according to World Health Organization counting criteria. The respirable dust was analyzed for the content of quartz, cristobalite and non-fibrous SiC using X-ray powder diffractometry (Føreland et al., 2008). The relationships between dust components and total dust were modeled and these models were applied on the historical measurements, for the development of a new, historical job exposure matrix (JEM). A historical JEM is a data file consisting of estimates of mean exposure levels to given exposure factors, for each job code, and each defined time period. The JEM developed for this study consists of estimates of exposure to total dust, respirable dust, respirable quartz, respirable cristobalite, respirable SiC, and SiC fibers, in addition to qualitative categories of exposure to PAH and asbestos, for each of the years 1913-2005, for up to 80 job groups distributed among the three Norwegian SiC plants.

The first author of the JEM study (SF) (Føreland et al., 2012) and the first author of Paper II and III (MDB) visited the three plants together, and interviewed experienced workers with extensive knowledge about present and historical production processes. Through a succeeding communication the two authors agreed on a common coding system for job codes in the JEM and in the cohort employment records.

11.2.3 Modeling of historical total dust exposure

By means of the existing total dust measurements a total dust JEM could be inferred including most job tasks in the furnace hall, processing, and maintenance departments, for the period 1967-2005. Multiple linear regression models were developed, using a forward blockwise entry procedure. The final model was the one that showed the best fit using the squared correlation coefficient, and contained the following blocks: Job group, Process related parameters, Five-year periods, and executing institution (NIOH). This last variable was a categorical variable assigned to measurements performed by the NIOH, because measurements performed by the plant personnel systematically showed higher exposure levels than the NIOH measurements. This phenomenon was interpreted as a sign of plant measurements mainly being performed to test compliance with the occupational exposure limits (OEL), and that job tasks known to be especially dusty were prioritized for these measurements. NIOH measurements, on the other side, were performed to show representative exposure levels of the plant, using a random sampling strategy. For five-year periods without any measurement data, the mean of the five-year periods before and after was used. For the period preceding 1967 (in the oldest plant) when no gravimetric measurement data were available, information about changes in job organization and technical improvements was used to estimate relative changes in exposure. For job groups not included in the measurement program, exposure was assessed using either other job groups with assumed similar exposure, similar job groups from one of the other plants, or a relative measure (low exposed = 10 % of the mean total dust exposure in the department, office workers = 1 % of mean total dust exposure at the whole plant). The development of the JEM is described in detail by Føreland et al. (Føreland et al., 2012).

11.2.4 Modeling of exposure to specific components

The parallel measurements of total and respirable dust, and total dust and fibers, were used to estimate the contents of the specific components relative to total dust, for each job group. Due to differences in workplace design and work organization, separate models for each plant were constructed. Mixed effect models were used, as each worker contributed with more than one measurement. Akaike's information criterion (AIC) was used to determine the model with the best fit, and the final model included *worker* as a random effect, and *total dust* and *job group* as fixed effects. Assuming that the proportions of the specific exposure factors in total dust were constant over time, exposures to each specific factor could be estimated for each job group and each year of exposure from the total dust model.

Four exceptions from the main rule of constant relative content were included in the model concerning the oldest plant; one was due to the introduction of spraying water on the quartz before mixing the raw mix. This change in routines happened about 1937, and was estimated to have reduced the quartz content of the dust to 40% of the previous level. In the years 1913-1927, corundum (aluminium oxide) was refined in the processing department in addition to SiC. The level of non-fibrous SiC in the processing department was estimated to be 50% in this period relative to the level of the following period. In 1952 the sorting area was moved out from the furnace into a separate building, changing the composition of the dust for the sorters, and in 2000 the mix area became an additional work task for the control room operator (Føreland et al., 2012).

11.2.4.1 Results under the limit of detection

The construction of the JEM with the specific components depended on the exposure measurements performed in 2002/2003, when exposure levels already were reduced to a fraction of the levels from the earlier periods of SiC production in Norway. In 2002/2003, several measurements gave results below the limit of detection (LOD). The greater part of these measurements showed positive analytical results, but below LOD for the method; whereas others gave a null result or a negative value. Especially the cristobalite analyses gave a rather high percentage of results below LOD. It was necessary to determine how to deal with these results, in order to get as reliable basis for the construction of the JEM as possible. Several methods for replacing values below LOD have been suggested, and in the first draft of the JEM article positive numbers below LOD were treated as they were observed (Analytical Methods Committee of the Royal Society of Chemistry, 1987), and null or negative numbers were replaced by a number representing the LOD/square root of 2 (Eduard, 2002). The epidemiological analyses in Paper II used the JEM based on this method. Paper II was submitted and accepted before it became clear that the article describing the JEM would not be accepted by *Journal of Occupational and Environmental Hygiene* (JOEH) using this method. The JEM paper was therefore revised, and in this new version of the paper, all values below LOD were replaced using a multiple imputation approach. However, the fraction of quartz and cristobalite measurements below LOD was very high in the processing and maintenance departments (60-93%), therefore only the quartz and cristobalite measurements from the furnace departments were modeled using the imputation procedure for values below LOD. In the processing and maintenance departments available measurements on department level for all plants were used to

compute a common quartz and cristobalite fraction of respirable dust. These fractions were used in the computations of historical quartz and cristobalite in these departments. The results were applied in construction of the revised JEM used in the epidemiological analyses in Paper III.

11.2.5 Construction of the JEM

11.2.5.1 JEM for the historical cohort study

A JEM for total dust, respirable dust, respirable quartz, cristobalite and SiC particles, and SiC fibers, was then constructed, for a total of about 80 job group-plant combinations, for each year since start of production until 2005. The estimated exposure levels of the specific factors were validated through comparison with the few historical measurements that were available of these factors. The results were deemed satisfactory. In addition, qualitative estimates of PAH and asbestos were added to the JEM, based on available information about exposures (for PAH, a division in three; work in the proximity of the furnace; other jobs in the furnace hall; work outside furnace hall, and for asbestos, a division in two; jobs with direct contact with asbestos before 1984, and other jobs).

11.2.5.2 JEM for the lung function study

The JEM for the lung function study (Paper IV) was constructed by MDB, and was based on total dust measurements registered in the JEM data base as having been performed in the period 1996-2005. The measurements were either performed by the NIOH as part of the comparative exposure assessment study (Føreland et al., 2008), or by the plant personnel as part of regular surveillance. Internal comparisons showed significant differences between the plant measurements and the NIOH measurements for some departments. As described in page 29 the NIOH measurements were assumed to be more representative, and it was therefore decided that when available, only the NIOH measurements should be used for the calculations. For job groups without NIOH measurements, the geometric means (GM) of the plant measurements were reduced by a factor corresponding to the department ratio between the NIOH and the plant measurements. At job group level, GM and geometric standard deviation (GSD) of available measurements were calculated, and arithmetic means (AM) were estimated from GM and GSD using the formula $AM=GM*\exp(0.5(\ln GSD)^2)$ (Seixas et al., 1988). For two job groups, considerable preventive measures were applied to reduce exposures during the actual period, and significant differences in exposure before and after the preventive measures were implemented were observed. For these two groups different

GM and AM for total dust exposure were applied before and after the preventive measures came in place. All other job groups were assumed to have had constant total dust exposure levels throughout the study period.

11.3 Study design

11.3.1 Study design - Cancer/mortality studies

The cohort was linked with the Cancer Registry using the unique Norwegian ID-number. For persons dead before 1960 no ID-number was available, and for these persons linking was performed manually using name and date of birth. Dates of death or emigration, dates of any cancer diagnoses, and diagnostic codes were added to the cohort. In the cancer study (Paper I and III) we received both cancer diagnoses for the cohort and national site-specific cancer rate data from the Cancer Registry of Norway. For the entire period of follow-up (1953-2008) cancer diagnoses classified according to a modified version of the World Health Organization's International Classification of Diseases (ICD-7), were available. No recoding of the diagnoses was therefore necessary.

Also for the mortality study (Paper II) dates of death or emigration (from Statistics Norway) were added to the cohort by the Cancer Registry, whereas death diagnoses (from the Cause of Death Registry) and dates of death for the cohort, in addition to national cause-specific mortality rates were obtained from the Norwegian Cause of Death Registry. The diagnoses were coded according to the ICD code system applied at the time of death. Therefore, to be able to compare mortality rates over the entire period of follow-up, we recoded the diagnoses into a common system, see Table 1.

Table 1: Grouping of death diagnoses, by period and ICD code systems

Code system	ICD 6 / ICD 7	ICD 8	ICD 9	ICD 10
Period	1951 - 1968	1969 - 1985	1986 - 1995	1996-2007
All causes	001-999	000-999	001-999	A00-Z99
Cancer	140-207	140-209	140-208	C00-C97
Circulatory diseases	330-334, 400-468, 782	390-458, 782.4	390-459	I00-I99
a) Ischaemic heart disease	420	410-414	410-414	I20-I25
b) Cerebrovascular disease	330-334	430-438	430-438	I60-I69
Respiratory diseases	240-241, 470-527	460-519	460-519	J00-J99
a) OLD	501-502, 241, 527	490-493	490-493, 496	J40-J46
b) Pneumoconiosis	523-524	515, 516	500-503, 505	J60-J64
c) Pneumonia	490-493	480-486	480-486	J12-J18
Digestive diseases	530-587	520-577	520-579	K00-K93
External causes	E800-E999	E800-E999	E800-E999	V01-Y89

After linking with the Cancer Registry, respective the Cause of Death Registry, name and personal ID-numbers were deleted from the cohort data base. Dates of birth were replaced by the date 15th, while the birth month and year were maintained. Each person was assigned a unique, random ID-number.

After the de-identification of the data, the cohort was then linked with the JEM using year and job code, and relevant exposure levels for all the exposure factors were assigned to each person time-weighted in accordance to duration of employment during the year. Each worker's cumulative exposure to each of the exposure factors could then be summed up over all years of employment.

11.3.2 Study design – lung function study

The survey was carried out through the practical assistance by the occupational health services at the plants, and was implemented in the regular health surveillance of the employees. At first inclusion in the lung function study the participants answered two questionnaires, the first about familial asthma, allergy, doctor diagnosed asthma, previous exposure, and smoking. The second questionnaire was used at every follow-up in the survey, and included questions about age, respiratory symptoms, smoking habits, current job title, and any job held during the past year. Up to three job titles with dates of start and end could be registered per person per year. Spirometry was conducted according to the recommendations from the European Community for Coal and Steel (ECCS) (Quanjer et al., 1993). The ECCS recommendations were also used in the quality assurance of the spirometers used in the study, and in the interpretation of the results (Quanjer et al., 1993). The technicians performing the examinations were trained especially for the study, and were followed up with regular courses during the study period. All the collected survey data were anonymized before they were transported to the researchers.

A job code system was developed by MDB, making the linkage between the survey data, with information on jobs held through the past year, and the JEM possible. Exposure to total dust was applied to each person-year relative to the duration of work connected with a job code during the year.

11.3.3 Presentation of exposure data

In the tables presenting the epidemiological analyses (Papers II and III), the corresponding levels of cumulative exposure were presented. In addition, a figure,

illustrating the mean levels of total dust exposure by department and 10-year periods, was published in Paper II, and a table with mean intensity of exposure to all exposure factors, by department, and before and after 1960, was supplied with Paper III, in order to illustrate the exposure levels for the workers in this cohort. In Paper II, a table also presented the mean cumulative exposures at end of follow-up, to all investigated exposure factors, stratified by department.

11.4 Statistical methods

The epidemiological analyses were performed using several parameters of exposure. In Paper I, written before the JEM was finished, different aspects of time were applied in the analyses. In Paper II and III, cumulative exposure derived from the historical JEM was used as tertile categories (high, medium and low) with equal numbers of person-years of follow-up in each tertile. Cumulative exposure was also log-transformed and used as a continuous variable in internal analyses. In Paper IV, current (last year's) exposure to total dust was used as the exposure variable in the analyses.

SIR and SMR were performed to compare the cancer and mortality incidence in our cohort with the general population. National rates for cancer by site, 5 year age groups and 5 year periods of diagnosis were provided by the Cancer Registry of Norway, and national mortality rates by cause of death, 5 year age groups and 5 year periods of death were provided by the Statistics Norway, the Cause of Death Registry. SIRs of site specific cancer were performed unstratified, stratified by duration of employment (Paper I and III), period of first employment (Paper I), time since first employment (Paper I), smoking status (Paper I), department (Paper III), and tertiles of cumulative exposure (Paper III). Ten and twenty years lag of exposure was applied in Paper III. Cause specific SMRs were performed with stratifications by department, duration of employment and tertiles of exposure (Paper II).

Internal comparisons in the cancer and mortality studies were performed with Poisson regression, using as reference group either the lowest tertile of cumulative exposure (Paper II and III) or the “Other, low exposed” department group (Paper III). Stratification by duration of employment was applied in Paper II, and some analyses were performed among ever-smokers only (Paper II and III). Time weighting of exposure as described by Jahr (Jahr, 1974) was applied for quartz, cristobalite and fibers, with and without a clearance factor assuming a 10 year half-life of the exposure substance (Checkoway et al., 1990)

(Paper III). Comparisons between the different specific exposure factors were performed with multivariate Poisson regression analyses using log-transformed cumulative exposure (Paper II and III), and 20 years lag of exposure (Paper III). The relative effects of the exposure factors were evaluated by studying how the effect estimate of one factor changed when a second factor was included in the model, and whether inclusion of a second factor contributed to a better fit of the model, according to the likelihood ratio test (LR-test) (Paper II and III). All the internal analyses were adjusted for age (Paper II and III). Adjustment for period of diagnosis was applied in Paper II.

STATA software was used in all analyses throughout Paper I-III.

Linear mixed models (LMM) were applied for the bivariate and multivariate analyses in Paper IV. FEV_1 and FVC per squared heights, FEV_1/h^2, and FVC/h^2, respectively, were the outcome variables, as recommended by others (Dockery et al., 1985; Ware and Weiss, 1996). Bivariate analyses using LMM were performed in three dust exposure groups corresponding to the tertiles of the GM of dust exposure levels among the workers. Time since inclusion in the study and age at inclusion were used as covariates. In the multivariate analyses, all covariates of interest were included in the initial model. Akaike Information Criterion (AIC) was chosen for the model selection, and the Autoregressive Moving Average covariance matrix for the fixed effect gave the best fit (lowest AIC), and was therefore the preferred model. Models containing fixed and random effects were reduced by elimination of non-significant covariates, unless the covariate was a covariate of interest, and the removal resulted in less than 20% change of the outcome estimate. Multivariate analyses were also performed stratified by smoking.

Statistical software used in Paper IV was SPSS and SAS.

12 Results and summaries of papers

12.1 Paper I

Paper I examines site specific cancer incidence, and lung cancer incidence specifically, among short-term and long-term workers (≤/> 3 years of total employment).

Altogether, among 2612 workers, 531 cancer cases were observed, compared to 424.9 expected cases, giving an SIR of 1.3 (95% CI 1.1–1.4). Short-term workers had an SIR of 1.4 (95% CI 1.2–1.6), and long-term workers had an SIR of 1.2 (95% CI 1.1–1.3). The most important single cancer site contributing to the observed excess was an increased lung cancer incidence with 103 cases versus the 51.7 expected (SIR 2.0, 95% CI 1.6–2.4), with SIRs of 2.6 and 1.7 among the short- and long-term workers, respectively. The sub-group "other and unspecified lung cancer" contained the major part of the lung cancer cases and was significantly increased among both short- (24 cases, SIR 4.4, 95% CI 3.0–6.6) and long-term workers (28 cases, SIR 2.4, 95% CI 1.7–3.5). No lung cancer cases occurred among never-smoking, short-term workers, and there was only one case among never-smoking, long-term workers.

The SIR of lung cancer related to duration of employment was significantly elevated for those with less than five years of employment. For longer employment durations, risk estimates were somewhat lower but still above unity. Among short-term workers, the risk estimate for the group "cancer, all sites except lung cancer" was higher for those with first employment in the more recent time periods, whereas for this group of sites the long-term workers had fairly stable, slightly elevated SIR irrespective of the period of first employment. In both sub-cohorts, lung cancer risk was significantly elevated in all periods of first employment except for workers employed after 1980, where only one lung cancer case was observed (in a long-term worker). The SIR for lung cancer was highest among those with first employment in the earlier periods, in particular among the short-term workers. The analyses stratified by time since first employment showed an increased lung cancer incidence ≥ 20 years after first employment, among both short- and long-term workers. Among the latter, the SIRs were the same regardless as to whether workers had been employed less or more than 10 years.

The short-term workers also had increased incidence of non-melanoma skin cancer, thyroid cancer, Hodgkin's lymphoma, and cancer at unspecified sites. Elevated SIR levels,

although non-significant, were seen for several others cancers sites, such as lip, esophagus, stomach, liver, pleura, and bladder. In the long-term worker group, there was an increased incidence of lip cancer and leukemia, in addition to a borderline increased incidence of prostate cancer. We also observed non-significant excesses of cancers of the stomach, nose, and skin.

12.2 Paper II

Paper II examines cause specific mortality over all, and specifically exposure related mortality from obstructive lung diseases, among long-term workers (> 3 years total employment).

Among 1687 long-term workers, an increased total mortality risk (SMR 1.1, 95% CI 1.0-1.2, 788 cases) was observed, with significantly increased risks of cancer (SMR 1.2), respiratory diseases (SMR 1.6), and external causes (SMR 1.5). Excess risks were, in addition, observed for the respiratory subgroups OLD (SMR 2.0), pneumonia (SMR 1.4), and pneumoconiosis (SMR 15). No excess risks were observed for circulatory diseases or diseases in digestive organs. The increased risk of mortality from OLD was linked to employment in the two production departments; furnace (SMR 2.7, 95% CI 1.6-4.6) and processing (SMR 2.2, 95% CI 1.2-4.3). There was no increase in mortality from OLD among workers with affiliation to the maintenance (SMR 1.0) and "other, low-exposed" (SMR 0.4) groups. Workers with employment in more than one department had a risk almost as high as furnace workers (SMR 2.5). Using three categories of cumulative exposure, the SMR of OLD was significantly increased at the two higher levels of exposure to total dust, cristobalite, SiC dust, and respirable dust, at all levels of exposure to fibers, and at the lowest and highest level of exposure to quartz. Internal analyses in models of ever-smokers using OLD as underlying cause of death showed significantly increased risks at the two higher levels of exposure to SiC (incidence rate ratio (IRR) 3.1 and 3.4 respectively), with a significant trend (p_{trend}=0.03). Using OLD as underlying or contributing cause of death the IRR estimates for SiC was somewhat reduced, still with a significant trend (p_{trend}=0.02). When using OLD as underlying or contributing cause of death we also observed a significant exposure-response trend for total dust (p_{trend}=0.03) and cristobalite (p_{trend}=0.05). Multivariate analyses including two log-transformed cumulative exposure variables in models of ever-smokers showed that SiC was the exposure factor with

the highest risk estimate when studied as an isolated log-transformed exposure factor. This risk estimate remained at the same level when fibers, quartz, or cristobalite were included in the model. SiC was, however, highly correlated to total dust (Pearson's correlation coefficient ($r_{Pearson}$) 0.88-0.93), and by including total dust in the model, the effect of SiC was reduced. Correlations between cumulative exposure to the investigated specific exposure variables were at a moderate level (≤ 0.75), except the correlations between quartz and fiber exposure ($r_{Pearson}$ 0.76-0.83).

There was a significant exposure-response trend for SiC dust among workers with less than 15 years employment. In multivariate analyses in this group of workers, the risk estimate was highest for SiC, and was not changed when other exposure factors were included in the model. Among workers with employment duration 15 years or more, there were significant exposure-response trends for total dust and cristobalite, and a borderline significant trend for quartz. In multivariate analyses risk estimates were highest and most stable for the two crystalline silica agents, cristobalite and quartz. When including both cristobalite and quartz in the model, the effect of quartz was reduced, and cristobalite seemed to be the most important factor. The inclusion of total dust did not change these estimates.

12.3 Paper III

Paper III examines exposure related lung cancer incidence among long-term workers.

The lung cancer risk among long-term workers was increased compared to the general male population (SIR 1.6, 95% CI 1.3, 2.1). The risk was highest among workers in the furnace department (SIR 2.3), and among those with employment from more than one department (SIR 1.9). Workers from the processing or maintenance departments had a non-significant increased risk of SIR 1.4, and the "other, low-exposed" group had an SIR of 0.6. Corresponding contrasts between the departments were seen in the internal analyses, using the "Other, low exposed" category as reference group, and adjusting for smoking, respective among ever-smokers only. Without adjustment for smoking the contrasts between "other, low exposed" workers and the other departments were larger (IRR for furnace 3.8). SIR analyses by categories of cumulative exposure factors showed significantly increased lung cancer incidences at the highest tertile of all the four specific exposure factors. Internal analyses among ever-smokers with the same exposure categories gave an increasing risk

with increasing exposure to all exposure factors, and a statistical significant test of trend for cristobalite and total dust. All risk estimates (both SIR and IRR) in the highest exposure groups increased when exposure was lagged 20 years, and significant tests of trend were observed for all exposure factors except quartz. With 10 years lag of exposure the results did not differ from the non-lagged analyses. Time-weighting of exposure ("Jahr model") did not give increasing risk estimates with increasing exposure levels. When a clearance factor with 10 year's half-life was added to the model, an exposure-response association was seen with cristobalite exposure, but no significant test of trend. There was no association between lung cancer incidence and the indicator of exposure to asbestos.

In the multivariate analyses using log-transformed cumulative exposure, only cristobalite, SiC and fibers were included, due to the high correlation ($r_{Pearson}$=0.84) between cristobalite and quartz, introducing collinearity. In preliminary analyses, with quartz in the models, the effect estimates of cristobalite and fibers increased considerably, whereas the effect estimate of quartz was reduced to about 0.5, indicating that the effects of both cristobalite and fibers were stronger than that of quartz.

The effect estimates of the other exposure factors were substantially reduced when cristobalite was added to the multivariate model. Adding cristobalite to a model already including SiC gave a significant LR-test, indicating a stronger effect from cristobalite. Adding fiber to a model including SiC reduced the effect of SiC and gave a significant LR-test, but somewhat weaker than cristobalite. The effect estimate of cristobalite was reduced and not longer significant when fibers were added to the model. The reduction of cristobalite estimate by fiber, however, was less than the reduction of the fiber estimate by cristobalite.

12.4 Paper IV

Paper IV examines the association between total dust exposure and annual change in FEV_1 and FVC.

The median total dust exposure of the employees did not change during the study period, and the prevalence of current smokers was highest in the groups with highest dust exposure. At inclusion, the FEV_1 and FVC in percentage of the predicted values were slightly lower in the highest exposed groups compared with the lowest exposed group. Both among nonsmokers and current smokers the annual decline in FEV_1 during follow up

appeared to be steeper in employees of the highest exposure groups compared to the lowest exposure group. This trend was less clear for FVC. In the multivariate analyses, where the outcome variables were FEV_1/h^2 and FVC/h^2, a dose-response relationship was observed between annual decline in FEV_1 and dust exposure. This decline was steeper in current smokers than in non-smokers, though this association was not significant. No corresponding association was found between annual change in FVC and current dust exposure or smoking. In analyses stratified by smoking a significant increased annual decline of FEV_1/h^2 was associated with increasing dust exposure levels both among non-smokers and current smokers. This effect was more pronounced in smokers than in non-smokers.

13 Discussion

13.1 Methodological considerations

13.1.1 Selection bias

13.1.1.1 Left censoring of the cohort

We are quite confident that employment data on workers that were employed in the industry in 1942 or later is satisfactorily complete, also in retrospect. We are, however, totally missing information about workers leaving the industry before 1942. The start of follow-up is 1st January 1951 (for the mortality study) respective 1953 (for the cancer study). This limits the cohort cross-sectionally, to workers still employed in 1942 and still alive at the start of 1951/1953. This so called left-censoring of a cohort induces a possible selection bias through a healthy worker effect – a survivor population (Checkoway, 1995). As exposure intensities were higher in the first decades of the Norwegian SiC production history, work related diseases and deaths would be expected to be more frequent in earlier years. In the Norwegian SiC industry, many silicosis cases were reported in the 1940-ies, and there is reason to believe that quite a few died from work related lung diseases, primarily silicosis, with and without tuberculosis, in the 10-20 years before 1950. These deaths are not counted in our study, and such possible effects of heavy exposure from these years are hidden from our knowledge. Some remains, however, of this "silicosis epidemic" is seen in the present cohort, see Figure 1, page 42.

Left censoring is a problem in epidemiologic studies because it may lead to dilution of the real associations (Checkoway, 1995). With respect to silicosis this is hardly a problem in our study, as we have a solid documentation of an increased mortality from silicosis in our cohort from these early years. The lacking cases from the years before 1951 make it difficult to perform analyses related to specific exposure factors, but the overall risk is documented well enough. With respect to lung cancer and OLD it may be a sign of a healthy survivor bias that we have registered only one death from OLD and no lung cancer cases in the 1950ies. It may on the other hand represent a change in disease pattern, as both lung cancer deaths and OLD deaths show a steady increase for several decades after 1951, whereas silicosis deaths decreases after a maximum in the 1960ies. In the period 1951-1969 we observed only three cases of OLD as underlying cause of death in the whole cohort of

short- and long-term workers, whereas four of the eight observed cases of silicosis in our cohort were observed in this same period. This possible change in disease pattern would be very interesting to study in the light of changes in exposures, but this, unfortunately, is difficult, due to the left censoring.

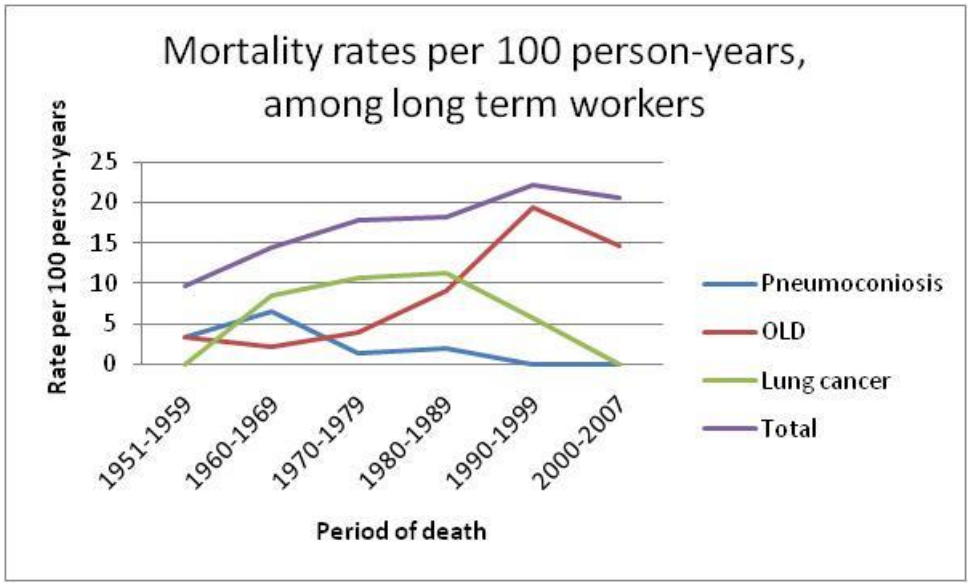

Figure 1: Mortality rates for selected causes of death in a cohort of 1687 long-term SiC workers.

The very low total mortality rate in the first years of follow-up could be due to changes in the age distribution of the cohort. In fact, only 5 percent of the cohort was over 70 years in the first ten years of follow-up (Figure 2, page 43). This is probably a result of the cohort being cross-sectionally started in 1942, with all cohort members being part of the working population at that time.

It is possible that the left-censoring of our cohort led to an underestimation of the cancer incidence and OLD mortality in the first years of follow-up because of the healthy survivor effect. On the other hand, we do not have any reason to believe that the left-censoring could imply an overestimation of the risk. Analyses with an inception sub-cohort starting 1951 showed that overall trends remained the same as in table 3, Paper II. Almost no deaths, however, were observed in the first 20 years of follow-up of this inception sub-cohort, and no pneumoconiosis deaths were observed, as all workers with pneumoconiosis as the cause of death had started work before 1950. A strength of our study is the long follow-up period, giving statistically significant estimates of effect in spite of the left censoring.

13.1.1.2 Missing register data

The start of follow-up in the mortality study is 1951, and start of follow-up in the cancer study is 1953. The Cancer Registry and the Cause of Death Registry are approximately complete, and linked to the Norwegian 11-digit ID-number, from 1960. The Norwegian ID-number was establish in 1964, and was given to all citizens alive after 1960. For cancer diagnoses and causes of death before 1960, a manual connection to the Cancer Registry and the Cause of Death Registry had to be done, using names and dates of birth. This work was done by one of the co-authors from the Cancer Registry of Norway (JIM). This dependence upon names and dates of birth before 1960, and lack of unique identification, in addition to possible upstart imperfections in the two registers, may have lead to some persons missing that should have been part of the cohort. We chose, however, to use the data we had, and not to limit the cohort to the more complete years after 1960. The possible loss of subjects is not believed to be dependent upon exposure or outcome.

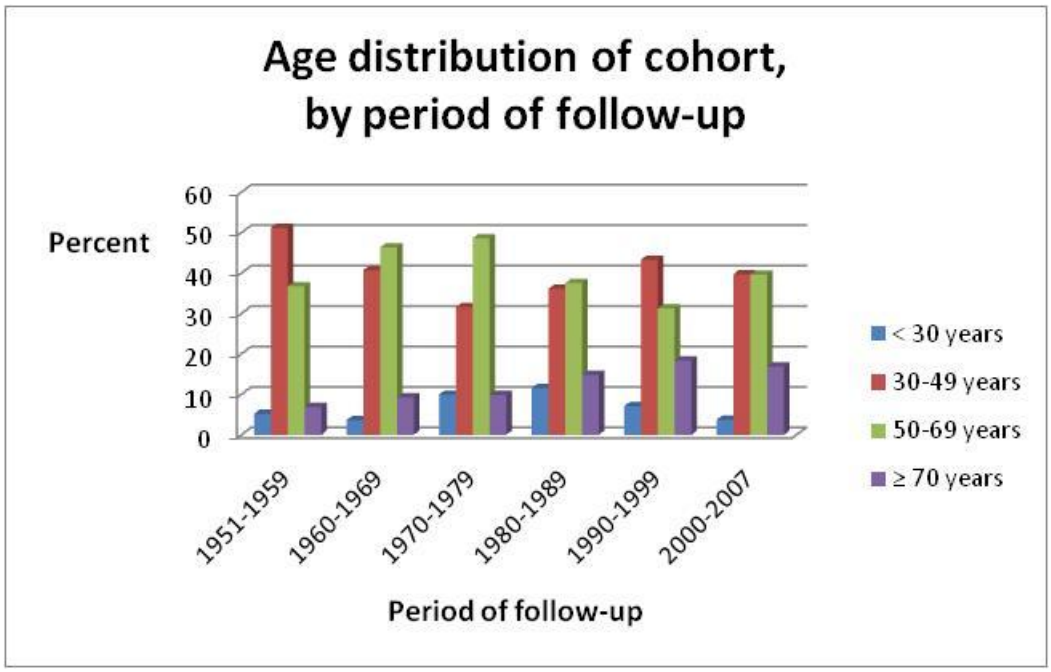

Figure 2: Age distribution, by period of follow-up, in a cohort of 1687 long-term SiC workers.

13.1.1.3 Possible selection bias in the lung function study

The lung function study had a very high participation rate when the study started, which probably secured the inclusion of a representative group of workers in the study. The fraction of included workers participating in follow-up examinations was reduced to 93% at

the second and 86% at the third examination, whereas only 34% participated in a fourth examination. The analysis method used, LMM, has the great advantage that all results can be included and contribute to the analyses, and the fact that several of the test results came from the same person and that test results from some years were missing was taken care of in the analyses. However, there is a possibility that there has been a selective dropout from the study, and that workers with lung symptoms related to work left their employment in the SiC industry during the study, giving a healthy survivor effect. Søyseth et al. has in two papers studied this problem, also in relation to the SiC industry, and they found that dropout from the study was related to reduced lung function (Soyseth et al., 2012; Soyseth et al., 2008). This being the case, there is reason to believe that the lung function loss related to dust exposure among SiC industry workers is even greater than the effect we have observed in this study.

13.1.1.4 Comparability - choice of reference population

We have in our study performed SIR and SMR analyses using the general population as reference population. This is a method that is much used in occupational epidemiologic studies. However, the general population has been assumed to be different from the working population in many ways, and therefore, in fact, unsuitable for the purpose. The line of reasoning is that the working population consists of people that are healthier than the general population, as the general population, in addition to workers, includes people that due to diseases and handicaps are not able to participate in the working life. Many studies have, in fact, shown that the standardized mortality ratios of several working populations, when compared to the general population, are less than 1 (Hernberg, 1992). This "Healthy worker effect" (McMichael, 1976) may therefore lead us to overlook low grade, but real, associations between exposures in work and disease, because we compare with a less healthy population.

The choice of office workers as reference group in the study of industry workers' diseases has also been much discussed and criticized. The inclusion of office workers in the control group may introduce two forms of selection bias, drawing in different directions. Firstly, white collar workers have traditionally belonged to a different social class than blue collar workers; they smoked less, and had a higher standard of living. Several studies have shown that white collar workers had a lower risk of lung cancer and several other cancers, and the mortality risk was also lower than among blue collar workers (Hall and Rosenman, 1991; Merlo et al., 2010). The second form of selection bias is that blue collar workers that

have got respiratory symptoms because of their job, may still be able to work in unexposed work, and they will then "pollute" the office worker group in the sense that they may be registered as "low exposed" office workers with the health problems of previously high exposed workers.

We have tried to encounter these potential biases in several ways. We performed our preliminary analyses including and excluding a group that was registered as only working in the office. These analyses gave similar results, so we chose to include the office workers in the cohort, in order to keep as much information (as many person-years) as possible in the study. In the internal exposure-response analyses we grouped the cumulative exposure by person-year tertiles. Thus, we had no non-exposed group, but ordinary office workers were included in a low exposed group, and office workers with previously exposed work were grouped according to their respective cumulative exposure. The exposure-response analyses with ever-smokers only (Paper II and III) also were performed in order to limit the effect of the non-smoking white collar workers on our exposure-response associations.

The comparisons with the general population which we used in the SIR/SMR-analyses may also be subject to criticism in the same direction. Particularly it has been suggested that industry workers smoke more than the general population, and that an increased incidence of lung cancer in an industry population would be due to this smoking excess only. This question has been discussed in several papers, and it has been demonstrated through analyses of simulated data that even if the smoking prevalence is higher among industry workers, only a limited excess of lung cancer in an industry population relative to the general population can be explained as due to more prevalent smoking (Axelson, 1980; Järvholm and Thiringer, 1980). Internal analyses related to dose estimates will represent an additive control of the findings. It has also been proposed that workers with the highest dust exposures also are the heaviest smokers, and that this will bias the exposure-response analyses. Siemiatycki et al. found that there was no correlation between smoking and dirty work, and concluded that internal analyses of "dose-response" in cohort studies are unlikely to be seriously confounded by smoking habits (Siemiatycki et al., 1988). However, at least in the recent years, heavy smoking among workers in the Norwegian SiC industry was associated with the highest level of dust exposure (Paper IV – table 1). Given that there was a risk of confounding by smoking in the internal analyses, we tried to encounter this problem with our analyses restricted to ever-smokers (Paper II and III). As we had no information about level of smoking/pack-years etc. in the historical cohort, there was uncertainty about how much of the smoking confounding that still

remained, but as our results were consistent between different analyses, they should be considered reliable.

13.1.2 Information bias

13.1.2.1 Non-differential misclassification

The detailed information about specific exposure factors available for the analyses in Papers II and III was based on advanced statistical modeling both of historical total dust exposure levels, and of the relations between total dust exposure and exposure from the specific dust factors respirable dust, cristobalite, quartz, SiC fibers and non-fibrous SiC. The results from the modeling are validated, both internally by cross-checking, and externally, by comparison with the existing measurements from earlier years. It is impossible to believe that such modeling will be without errors. On the other hand, as the JEM was developed without knowledge of the job tasks of persons who had developed diseases we assumed that the exposure assessment errors were independent of the outcomes of the study. The misclassification associated with the JEM development would therefore be non-differential, which most likely give a regression towards the null (Checkoway, 1995; Kirkwood and Sterne, 2006). The positive results we have found in the study are, therefore, likely to be reliable. The modeling of historical exposure to specific exposure factors was based on the assumption (with a few exceptions) that the relative content of the specific exposure factors in total dust in each job group had been constant during all years of production. Given that this assumption was correct our findings of the relative importance from the exposure factors should also be reliable, even though the values of the IRRs may not have been completely accurate.

The exposure data in Paper IV was derived directly from total dust measurements from the same period as the lung function measurements were performed. Only total dust was included in the JEM used in this study, as the study was part of a larger project in the Norwegian smelting industry, and total dust was the only exposure metric available in many of the other companies (Johnsen et al., 2010; Soyseth et al., 2011a). As the GM of total dust in some job groups differed significantly between measurements done by the plant personnel and by the NIOH, the measurements done by the NIOH were chosen as the basis of the JEM. Where no NIOH measurements were available for a job group, the plant results were adjusted with a factor corresponding to the ratio between GM of NIOH measurements and GM of plant measurements in the department. The reason for such prioritizing of NIOH measurements was that when there were differences, the plant measurement levels were

higher, and plant personnel confirmed that these measurements often were done by job groups and during tasks where dust levels were believed to be especially high, to check whether the exposures where within OELs. The NIOH measurement program was designed to be representative for job groups and job tasks. There was a risk of introducing a bias by choosing the NIOH measurements when the differences were statistically significant, if the "worst case" measurements in fact were more representative for the total working environment than the final results mirror, and the actual dust levels were higher than the JEM tells. The consequence of this would be that the observed health effects became associated with an artificially low dust level. Contrarily, if the NIOH measurements were more correct than the plant measurement levels, earlier studies may have associated health effects with an artificially high dust level, thus underestimating the effect of the exposures.

13.1.2.2 Dust measurements in the exposure assessment study

Even though there is a mixture of many airborne exposure factors in the SiC industry, especially in the furnace hall, four specific exposure factors, in addition to total and respirable dust, were chosen for closer study in this project, on the basis of previous knowledge and suspicions about health effects. As discussed in section 10 (page 20), quartz and cristobalite are exposure factors associated with silicosis and COPD, and they are classified as carcinogenic to humans. SiC fibers have resembled asbestos fibers in many toxicological studies, and have in previous studies in the SiC industry been associated with an increased lung cancer risk. SiC particles are the primary product of the industry, and were chosen from that reason, even though no suspicion of specific toxicity was linked to this exposure, because this agent is important for subsequent use of the finished products.

There are other exposures in the working environment in the SiC industry which we have not considered in detail in this study. SO_2 gas was considered as a potential risk factor for respiratory disease at the start of the study, and some measurements were performed in 2002/2003 to assess the level of exposure (Føreland 2008), which was shown to be generally low at that time, but with some peak exposures occurring. It would be expected that the levels of exposure have been higher in earlier days, because the sulfur content of the coke has been reduced due to regulations. However, there were no historical measurements of SO_2 available for the modeling of historical exposures, and therefore the substance could not be included in the JEM.

CO gas is a continually monitored health risk in the furnace hall, with all workers having a CO meter with an alarm. This exposure, however, is primarily associated with

sudden death from poisoning at high exposure levels, and secondly, a possible increased risk of heart disease. As the primary focus of the present project was lung diseases, CO gas monitoring was not prioritized.

The exposure to carbonaceous dust in the furnace hall represents a considerable fraction of the total dust exposure, and analyses relative to this exposure could be desirable. It was decided to not include organic dust in the analyses, firstly because coke or graphite dust is not known to represent any danger to health, secondly because PAH has been measured at some instances in the furnace hall, and the mean levels of exposure were shown to be relatively low, and thirdly because a measurement program of these dust fractions, with the same quality of detail as the other dust fraction measurements, would become too expensive to be feasible. Some measurements had shown high levels of exposure to PAH among crane-men prior to the introduction of air-ventilated crane cabins. This is in accordance with other studies (Smith et al., 1984). Only one lung cancer case in our study base had worked in the crane in the actual period (before 1953). In addition, other cancer sites associated with PAH exposure, such as bladder cancer, was not elevated (Romundstad et al., 2001) (Paper I) – indicating that PAH probably not was an important carcinogen in the SiC industry.

We had no quantitative historical information about asbestos exposure, and we therefore chose to use a qualitative estimate of asbestos exposure related to certain tasks, based on information from experienced workers at the plants. Asbestos was used for many purposes in the SiC industry before it was prohibited in Norway in 1984, but it was mainly used by maintenance and furnace workers from 1940-1980 (Føreland et al., 2012). The description is coarse and misclassification is possible. However, as we found no association between asbestos exposure and lung cancer, we assume that other exposure factors were more important.

13.1.2.3 The role of particle size

Traditionally, exposure measurements in the working environment have been based upon so called "total dust" measurements, and these measurements represent an important basis of the JEM developed for this study. The dust fraction called total dust is a fraction that is shown to lie in between the inhalable and the thoracic fraction of the dust (Davies et al., 1999). The current ideal for measurements with respect to analyses of the associations with obstructive lung diseases, and probably for bronchogenic lung cancer, would be the thoracic

fraction of the dust (the fraction of the inhaled aerosol that goes past the larynx and penetrates into the lung) (Vincent, 2007), as these diseases primarily are located in the thoracic section of the respiratory system. However, the measurements in the comparative study should as much as possible resemble the measurements performed in the industry in earlier days, and the actual filter cassette (37-mm Millipore cassette) was chosen because this has been a standard for many years. Besides, in Paper IV total dust was used as the exposure metric in the analyses. This paralleled the analyses performed in other smelter industries in the same project (Johnsen et al., 2010), and made comparisons with these other industries possible. Even though the "real" exposure level relevant to the target organ is not achieved, the possibility to compare with the exposure levels in other studies is a great advantage.

For pneumoconiosis, as a disease located in the alveolar regions of the lung, the respirable fraction of the dust has been identified as most relevant. Respirable dust is a size fraction of the dust corresponding to the part of the inhaled dust that penetrates all the way down to the alveoli (Vincent, 2007). Also for lung cancer originating in the peripheral parts of the airways, respirable dust may be a relevant dust fraction to measure. Analyses of crystalline silica have traditionally been performed in the respirable fraction of the dust. It would perhaps have been interesting to know the thoracic cristobalite fraction when bronchial lung cancer is concerned, and also in relation to OLD and changes in FEV_1. However, other studies have measured cristobalite or crystalline silica in respirable dust only (Hnizdo and Vallyathan, 2003; Rice et al., 2001). By using crystalline silica from the respirable fraction we were thus able to compare with other studies.

Additional analyses of specific agents in the thoracic dust fraction would have required the collection of thoracic samples, doubled the number of x-ray analyses of crystalline dust fractions, and would also require adjustments of the analytical methods. Our study did not have these resources.

13.1.2.4 Measurements below the level of detection

As described in chapter 11.2.4.1 (page 30) two methods for handling measurement results below LOD are applied in JEMs used in this study. Paper II was kindly accepted by *Occupational and Environmental Medicine* before the concepts of how to deal with values < LOD were changed and the JEM paper was published, and as a consequence the JEM used in Paper II is different from the final JEM, used in Paper III. We have for comparison

reasons performed the analyses in Paper II with the final JEM, and the main tables are printed below (Table 2, page 51 and Table 3, page 52).

The new tables show a higher correlation between the exposure factors than the corresponding tables in Paper II, making it more difficult to separate the effects of the different agents. The associations between exposure factors and OLD mortality are not quite as convincing (less significant, larger confidence intervals) as in Paper II. However, we can still observe the overall tendency of OLD showing the more constant association with SiC exposure among workers with less than 15 years of employment, and with cristobalite among workers with more than 15 years of employment. In the "new" multivariate table (Table 3) we also see an association between OLD and SiC fibers of similar strength as that of cristobalite among workers with more than 15 years' employment, which was not observed in the corresponding table in Paper II.

13.1.3 Confounding

13.1.3.1 Smoking

Some aspects of internal validity could be discussed several places. The smoking aspect is discussed earlier, in connection with choice of reference population. There are, however, more than one important aspects connected to confounding by smoking.

Checkoway (Checkoway, 1995) suggests that smoking rather than to be controlled for as an ordinary confounder, should be viewed as a possible effect modifier. It is argued that very few people get lung cancer without having smoked, and that smoking is a too important cause of lung cancer just to be adjusted for. As a consequence smoking should be treated as an effect modifier, increasing the effect of dust exposure, whereas also dust may be an effect modifier of the smoking effect. As a result, highly dust exposed smokers may get more disease than both smokers without exposure and exposed without smoking. A robust method of testing effect modification is performing the analyses stratified by the suggested effect modifier. We have performed some of our analyses in the sub-cohort of ever-smokers, whereas the sub-cohorts of never-smokers and unknown smoking status contain too few cases to perform analyses of the dust effect in these sub-cohorts. Therefore, the question of to which degree smoking is an effect modifier is difficult to answer in our study.

Table 2: SMR and IRR of OLD-u and OLD-uc by cumulative exposure groups, using the revised JEM published in JOEH. (Corresponds to Table 3, paper II)

	All employees (N=1687)		All ever-smokers (N=1162)						< 15 years employment, ever-smokers (N=1114)			≥ 15 years employment, ever-smokers (N=599)		
	OLD-u (45 cases)		OLD-u (38 cases)			OLD-uc (55 cases)			OLD-uc (32 cases)			OLD-uc (23 cases)		
	SMR	95% CI	IRR*	95% CI	P_{trend}	IRR*	95% CI	P_{trend}	IRR*	95% CI	P_{trend}	IRR*	95% CI	P_{trend}
Total dust														
Low	1.4	0.7-2.8	1			1			1			1		
Medium	2.6	1.6-4.2	2.8	0.9-8.5		1.7	0.7-4.1		1.3	0.5-3.5		2.2	0.2-23.9	
High	1.9	1.2-3.0	2.6	0.9-7.7	p=0.2	2.5	1.1-5.8	p=0.02	2.3	0.8-6.5	p=0.09	5.3	0.7-39.9	p=0.02
Respirable dust														
Low	1.5	0.8-2.9	1			1			1			1		
Medium	2.7	1.8-4.3	1.9	0.8-5.0		1.2	0.6-2.7		1.0	0.4-2.5		1.1	0.2-7.9	
High	1.7	1.1-2.8	1.5	0.6-3.9	p=0.5	1.6	0.8-3.2	p=0.2	1.8	0.7-4.6	p=0.3	2.3	0.5-9.8	p=0.1
SiC fibers														
Low	2.2	1.3-3.6	1			1.0			1			1		
Medium	1.9	1.1-3.3	0.8	0.3-2.0		0.6	0.3-1.3		0.5	0.2-1.2		1.5	0.3-8.0	
High	1.9	1.2-3.0	1.1	0.5-2.5	p=0.7	1.1	0.6-2.0	p=0.7	1.1	0.5-2.4	p=0.9	2.4	0.5-10.3	p=0.2
SiC dust														
Low	0.8	0.3-1.9	1			1.0			1			1		
Medium	2.7	1.7-4.3	2.8	0.9-8.5		1.5	0.7-3.3		1.3	0.5-3.2		2.2	0.4-10.7	
High	2.3	1.5-3.5	3.3	1.1-9.8	p=0.04	2.1	1.0-4.5	p=0.04	2.5	1.0-6.2	p=0.05	2.7	0.6-12.0	p=0.2
Quartz														
Low	1.9	1.1-3.4	1			1.0			1			1		
Medium	1.8	1.1-3.2	0.8	0.3-2.2		1.0	0.4-2.2		0.7	0.3-1.6		2.5	0.3-24.0	
High	2.1	1.4-3.3	1.4	0.6-3.3	p=0.3	1.7	0.8-3.5	p=0.1	1.5	0.6-3.6	p=0.3	5.3	0.7-40.0	p=0.02
Cristobalite														
Low	1.6	0.9-3.0	1			1.0			1			1		
Medium	2.1	1.3-3.5	1.2	0.5-3.0		1.2	0.5-2.5		1.1	0.5-2.6		2.2	0.3-19.2	
High	2.1	1.4-3.3	1.6	0.7-4.0	p=0.2	1.7	0.8-3.5	p=0.1	1.4	0.6-3.4	p=0.5	4.5	0.6-33.6	p=0.04

* Adjusted for age (</≥ 75 years), and period of diagnosis (</≥ 1 Jan. 1990)

Table 3: IRR of OLD-uc, using log-transformed cumulative exposures, adjusted for age, period of diagnosis, and other exposure factors, by duration of employment, using the revised JEM published in JOEH. (Corresponds to Table 4, Paper II)

	All N=1162, 55 cases, 30474 PYR				< 15 years employment duration N = 1114, 32 cases, 18899 PYR				≥ 15 years total employment duration N = 599, 23 cases, 11574 PYR			
	IRR*	95% CI	LR-test†	$r_{Pearson}$	IRR*	95% CI	LR-test†	$r_{Pearson}$	IRR*	95% CI	LR-test†	$r_{Pearson}$
SiC fibers	1.3	0.8-2.0			1.0	0.5-1.9			3.1	1.3-7.5		
Fibers adjusted for quartz	0.9	0.4-1.7	p=0.1	0.77	0.7	0.3-1.6	p=0.2	0.70	2.2	0.7-7.0	p=0.4	0.80
Fibers adjusted for cristobalite	0.7	0.4-1.4	p=0.02	0.76	0.6	0.2-1.4	p=0.08	0.72	1.8	0.5-6.2	p=0.2	0.78
Fibers adjusted for SiC	1.0	0.6-1.7	p=0.03	0.51	0.9	0.4-1.7	p=0.02	0.40	2.8	1.1-7.2	p=0.5	0.55
SiC particles	1.7	1.1-2.7			2.0	1.1-3.7			1.9	0.9-4.0		
SiC adjusted for quartz	1.6	0.9-2.6	p=0.4	0.64	1.9	1.0-3.7	p=0.6	0.54	1.3	0.6-3.0	p=0.05	0.71
SiC adjusted for cristobalite	1.4	0.8-2.5	p=0.3	0.75	1.9	0.9-4.0	p=0.9	0.69	1.0	0.4-2.5	p=0.03	0.78
SiC adjusted for fibers	1.7	1.1-2.8	p=0.9	0.51	2.0	1.1-3.8	p=0.7	0.40	1.3	0.5-3.2	p=0.03	0.55
Quartz	1.6	1.0-2.6			1.5	0.7-3.2			2.8	1.2-6.8		
Quartz adjusted for cristobalite	1.1	0.5-2.4	p=0.2	0.84	1.1	0.4-3.3	p=0.4	0.79	1.6	0.4-6.0	p=0.1	0.87
Quartz adjusted for fibers	1.8	0.9-3.6	p=0.7	0.77	1.9	0.7-4.8	p=0.4	0.70	1.7	0.5-5.6	p=0.2	0.80
Quartz adjusted for SiC	1.3	0.7-2.3	p=0.08	0.64	1.2	0.5-3.2	p=0.04	0.54	2.6	1.0-6.9	p=0.5	0.71
Cristobalite	1.7	1.1-2.7			1.5	0.8-2.8			2.8	1.3-5.9		
Cristobalite adjusted for quartz	1.6	0.8-3.3	p=0.9	0.84	1.4	0.6-3.2	p=0.8	0.79	2.1	0.7-6.3	p=0.5	0.87
Cristobalite adjusted for fibers	2.2	1.1-4.3	p=0.3	0.76	2.1	0.9-5.1	p=0.2	0.72	1.9	0.7-5.5	p=0.3	0.78
Cristobalite adjusted for SiC	1.4	0.8-2.5	p=0.2	0.75	1.1	0.5-2.4	p=0.07	0.69	2.8	1.2-6.9	p=1.0	0.78

† LR-test: Likelihood ratio test comparing the model containing one exposure factor with a model containing two exposure factors.

13.1.3.2 Variation in results related to aspects of time

13.1.3.2.1 Period of first employment

In Paper I we showed that the SIR of lung cancer among long-term workers was highest (SIR 2.1) among those employed in the period 1913-1959, somewhat reduced (SIR 1.7) in the next period (1960-1979), and in the last observation period (1980-2005) only one lung cancer case was observed, with an SIR of 1.0. Our comment in Paper I was that it was too early to conclude about lung cancer incidence in this last period, because of the long induction and latency period of lung cancer. Table 4 shows the development of lung cancer SIR in more detail, related to overlapping 20-year periods of first employment. A reduction in SIRs is suggested, but the tendency is too weak to draw any conclusions.

Table 4: SIR of lung cancer among long-term workers, by overlapping 20-year periods of first employment

Period of first employment	N	Person-years	Obs	Exp	SIR	95% CI
1930-1950	217	6661	14	7.6	1.8	1.1-3.1
1940-1960	288	9537	22	11.3	1.9	1.3-3.0
1950-1970	524	16007	30	18.7	1.6	1.1-2.3
1960-1980	761	21307	27	19.3	1.4	1.0-2.0
1970-1990	712	16965	14	9.1	1.5	0.9-2.6
1980-2000	443	7771	2	2.3	0.9	0.2-3.4

13.1.3.2.2 Short-term workers

In Paper I we chose to stratify the cohort by employment duration over and under three years. The background for doing this was that short-term workers in many studies show a higher risk of both lung cancer and mortality from several causes (Boffetta et al., 1998; Ronneberg, 1995). We wanted to avoid influence from factors outside the SiC industry that could interfere with the exposure-related analyses. Our results from Paper I gave a clear indication that also in this cohort the short-term workers had a risk pattern that diverted from the long-term workers'. There was an increase in cancer at sites related to alcohol and tobacco use, such as oral and pharyngeal cancer and lung cancer. In addition we found an increase in lung cancer without specific histology and also an increase in cancer, other sites. These two last classifications, with sparse information about diagnosis, are typically related to limited contact with the health service, and probably with low social class.

The short-term workers in our cohort also show the same tendency with regard to mortality, with high SMRs from several causes, among these cancer, respiratory diseases (mainly OLD), cerebrovascular diseases, and external factors, see Table 5.

The excess of lung cancer in the short-term worker group was assumed not to be connected with occupational exposures in the SiC industry. Inclusion of the short-term workers in the analyses using cumulative exposure could give rise to a potential bias, diminishing any exposure-response associations. Table 6 and Table 7 (page 56) show SIR and IRR of lung cancer related to department affiliation and categories of exposure factors using the whole cohort of both short- and long-term workers. The results are in accordance with the above assumption; with no significant contrasts between departments, or between levels of exposure, even though the power of the analyses is increased due to the increased number of cases and person-years.

Table 5: Cause specific mortality among short-term and long-term workers

	Short-term workers*			Long-term workers†			All workers‡		
	Obs	SMR	95% CI	Obs	SMR	95% CI	Obs	SMR	95% CI
All causes	462	1.4	1.3-1.6	788	1.1	1.0-1.2	1250	1.2	1.2-1.3
Cancer	116	1.5	1.2-1.8	201	1.2	1.0-1.4	317	1.3	1.1-1.4
Circulatory	177	1.2	1.0-1.4	347	1.0	0.9-1.2	524	1.1	1.0-1.2
Ischemic	92	1.1	0.9-1.3	176	0.9	0.8-1.1	268	1.0	0.9-1.1
Cerebrovascular	47	1.5	1.2-2.1	76	1.1	0.9-1.4	123	1.2	1.0-1.5
Respiratory	47	2.0	1.5-2.6	91	1.6	1.3-2.0	138	1.7	1.5-2.0
OLD	33	3.4	2.4-4.8	45	2.0	1.5-2.7	78	2.4	1.9-3.0
Pneumoconiosis	1	4.7	0.7-33.4	7	14.7	7.0-30.9	8	11.6	5.8-23.3
Pneumonia	12	1.0	0.6-1.8	38	1.4	1.0-1.9	50	1.3	1.0-1.7
Digestive	11	1.5	0.8-2.8	17	1.1	0.7-1.7	28	1.2	0.8-1.8
External	30	1.9	1.3-2.7	44	1.5	1.1-2.0	74	1.6	1.3-2.0
Other	81	1.7	1.4-2.1	88	0.9	0.7-1.1	169	1.1	1.0-1.3

* Start of follow-up one year after end of employment. N=923, 24200 person-years of follow-up

† Start of follow-up after 3 years of total employment. N=1687, 42689 person-years of follow-up

‡ Follow-up according to follow-up in the subgroups. N=2610, 66889 person-years of follow-up

Table 6: SIR and IRR of lung cancer in the whole cohort of short- and long-term workers, by department.

Department	N	Person-years	Obs	SIR	95% CI	IRR	95% CI
All	2612	67225	109	2.0	1.6-2.4		
Furnace	767	19556	44	2.6	1.9-3.5	2.1	0.8-5.3
Processing	578	13835	20	1.9	1.2-2.9	1.5	0.6-4.1
Maintenance	517	13366	15	1.4	0.9-2.4	1.2	0.4-3.2
Other, low exposed	225	6396	5	0.9	0.4-2.1	1.0	Ref
Mixed employment	525	14073	25	2.1	1.4-3.1	1.8	0.7-4.7

We started the follow-up of short-term workers one year after end of employment, as we wanted to exclude workers who left the employment because of death or disease. Nineteen short-term employees died or emigrated before start of follow-up, 10 of these died, and 9 emigrated. The causes of death for the 10 workers were cardiovascular diseases (4), suicide (2), car accident (2), diabetes mellitus (1) and cancer (1). Seven of the ten were still employed at the time of death. The assumption that these persons ended their employment because of disease or death, seem to be over all correct.

13.1.3.2.3 Induction and latency time. Long-term exposure.

Induction and latency time means that a certain time is necessary for an exposure to start the disease process (induction), and further time is necessary from the disease process starts until it is manifested as a recognizable disease (latency) (Checkoway et al., 1990). Lung cancer is a disease which is assumed to have an induction and latency time of 10-20 years. Exposures closer in time to the disease manifestation than 10-20 years are therefore assumed to have had no influence on the development of the disease, and it is common in exposure-response studies of lung cancer to null out the exposures of the last years. We have in Paper III reported the results of SIR- and IRR-analyses with 20 years exposure lagging. In our study 20 years exposure lagging means that the cumulative exposure level of a certain person-year is set to the cumulative exposure level of the same person 20 years earlier. We observed that all effect estimates were as high as or higher than the un-lagged estimates, and most exposure-response trends became statistically significant with 20 years lagging of exposure. We interpreted this as an additional confirmation of an exposure-response relationship. Ten years lagging of exposure did not have the same effect, implying that the induction and latency time of lung cancer is longer than 10 years. Another way of assessing the effect of lag time, when no exposure data are available, is analyses related to time since first exposure. We performed such analyses in Paper I, and also here we showed an increased lung cancer incidence $\geq$ 20 years after first employment.

Based on the thought that some exposure factors have a longer biological half-life than other factors, a suggested method for taking particle retention into account is Jahr's time weighting method (Jahr, 1974). This method was constructed with the purpose to study the association between crystalline silica exposure and silicosis development and assumed no particle clearance. The method has later been proposed by Checkoway for use in cancer studies (Checkoway et al., 1990). In the lung cancer study (Paper III) we tried this method, but we could not reproduce the clear associations we had found without the

Table 7: SIR of lung cancer in the whole cohort of short- and long-term workers, and IRR of lung cancer among ever-smokers in the whole cohort, by categories of exposure factors. IRR are adjusted for age.

	All employees (N= 2612, 67225 Person-years)					Ever-smokers (N=1527, 40720 Person-years)					
Total dust	N	Person-years	Obs	SIR	95% CI	N	Person-years	Obs	IRR	95% CI	P_{trend}
Low	892	20910	29	1.9	1.3-2.7	394	8863	17	1.0		
Medium	1444	21858	31	2.0	1.4-2.8	980	13860	20	0.8	0.4-1.6	
High	1036	24458	49	2.0	1.5-2.6	746	17997	46	0.9	0.5-1.6	p=0.9
Respirable dust											
Low	855	20968	29	1.9	1.3-2.7	361	8768	18	1.0		
Medium	1486	21700	31	2.0	1.4-2.8	997	13609	19	0.7	0.4-1.4	
High	1060	24557	49	2.0	1.5-2.7	776	18343	46	0.9	0.5-1.5	p=0.8
Quartz											
Low	927	20498	27	1.8	1.3-2.7	411	8514	16	1.0		
Medium	1385	22392	37	2.2	1.6-3.0	922	14135	24	0.9	0.5-1.6	
High	1037	24335	45	1.9	1.4-2.5	758	18071	43	0.9	0.5-1.5	p=0.7
Cristobalite											
Low	906	20745	29	1.9	1.3-2.7	418	8973	18	1.0		
Medium	1347	22474	30	1.8	1.3-2.6	889	14349	19	0.7	0.4-1.3	
High	1041	24006	50	2.1	1.6-2.8	744	17399	46	1.0	0.6-1.7	p=0.8
SiC											
Low	922	21385	28	1.8	1.2-2.6	436	9775	16	1.0		
Medium	1307	21697	31	1.9	1.3-2.7	871	13818	22	0.9	0.5-1.8	
High	1055	24143	50	2.2	1.6-2.8	742	17127	45	1.2	0.7-2.1	p=0.5
SiC fibers											
Low	1055	20734	25	1.7	1.1-2.5	506	8702	11	1.0		
Medium	1362	22207	39	2.3	1.7-3.2	905	13872	29	1.7	0.8-3.3	
High	980	24284	45	1.9	1.4-2.5	718	18146	43	1.4	0.7-2.6	p=0.6

method. Checkoway suggested a modification of the Jahr model, where the clearance of particles also is taken into account (Checkoway et al., 1990). By applying this method, assuming a 10 year half-life of the exposure substance in the organism, an exposure-related increase of IRR was observed for cristobalite, but with no significant trend. No exposure-related increases were observed for fiber or quartz exposure, see Table 8. Given the consistent results from the non-lagged and 20-year lagged analyses, we assume that the Jahr model does not describe the particle retention relevant for lung cancer development in a representative way. It is possible that other mechanisms act in connection with development of silicosis than of lung cancer, and that the aspect of high exposures in earlier days is not so important in lung cancer development mechanisms as in silicosis development. In a recently published study the Jahr time-weighted method was compared to ordinary cumulative exposure in a cohort study of silicosis among North Carolina Dusty trades workers and a cohort study of lung cancer among Chinese miners and pottery workers (Rice et al., 2011). The results confirmed the results from the original studies, an association between silica exposure and silicosis, and no consistent association with lung cancer. To our knowledge, no other study has applied the method in relation to lung cancer.

Table 8: Lung cancer incidence related to categories of time-weighted exposure, with and without a clearance factor assuming 10 years half-life of particles in the organism. Long-term workers, N=1687.

		Jahr-categories			Clearance with 10 year half-life		
		IRR	95% CI	p_{trend}	IRR	95%CI	p_{trend}
Cristobalite	Low	1.0			1.0		
	Medium	0.9	0.4-1.9		1.2	0.6-2.5	
	High	1.2	0.6-2.3	p=0.5	1.6	0.9-3.1	p=0.1
SiC fibers	Low	1.0			1.0		
	Medium	0.7	0.4-1.5		0.6	0.3-1.2	
	High	1.0	0.5-1.7	p=1.0	1.2	0.7-2.1	p=0.4
Quartz	Low	1.0			1.0		
	Medium	0.9	0.5-1.6		1.4	0.7-2.7	
	High	0.7	0.4-1.3	p=0.3	1.0	0.5-1.9	p=0.9

Crystalline silica has the ability to accumulate in the lung. Because of the relatively low crystalline silica exposure levels in the SiC industry it could be hypothesized that a certain period of exposure would be necessary for a sufficient amount of crystalline silica to accumulate, in order to induce any lung injury. Another way of handling the long term effects of exposure was to stratify the exposure related analyses of OLD by duration of exposure (over/under 15 years). Assuming that no effect would be discernible after only a

few years' exposure to low levels of crystalline silica, we wanted to see if through this stratification there could be a possibility to discern an effect of long term low level exposure to crystalline silica from the acute effects, probably caused by other factors. We found in Paper II an association between cumulative cristobalite exposure and OLD mortality among workers with more than 15 years of employment. Though the results have to be interpreted with some caution, especially as the modification of the JEM weakened the associations, we think this is an interesting finding.

13.1.3.2.4 "Sick worker turn-over effect"

We observed in Paper II that OLD mortality was associated with cumulative exposure to SiC among workers with less than 15 years of employment in the SiC industry, and with cumulative exposure to cristobalite among workers with more than 15 years of employment. One potential interpretation is that this is a special form of the healthy worker effect: A certain part of the worker population get respiratory symptoms/respiratory disease as a result of high levels of irritating dust (SiC, total dust load), and leave the plant before 15 years of employment. A healthy worker group stays on in the production, for up to 30 years, some of these exposed to low levels of crystalline silica all the time, most probably without any symptoms in the first years, but as the dust accumulates in the airways, it may ultimately induce a detrimental health effect. As the inflammatory effects of cristobalite are known to be more marked than those of quartz, it makes sense that we see associations between OLD mortality and cumulative exposure to cristobalite more than quartz, among these workers. It may seem a paradox, but a cristobalite related increased OLD mortality was in fact observed only among the "healthy workers" staying for a long time in the industry, whereas among another group of workers the dust exposure from SiC may have induced a "sick worker turn-over" effect.

13.1.3.2.5 Stratification by tertiles of exposure

We have, both in Paper II and Paper III, performed SIR/SMR analyses and internal analyses using tertiles of cumulative exposure to the investigated exposure factors. The tertiles were divided by number of person-years of follow-up in each group. The choice of dividing factor was according to custom at the Cancer Registry, and was done *a priori*. Other dividing factors could be e.g. similar number of cases in each group, or assumptions about effect-giving exposure levels. In Paper II we referred to supplemental analyses using the number of OLD cases as dividing factor. The results of these analyses were equivalent to

the results in the tables. Another option could be to divide the groups based on cumulative exposure groups with presumed high, medium, and low risk of disease. We had no such presupposition, and considered a division based on arbitrarily chosen cut-points to be potentially vulnerable to collapse in the analyses, whereas the person-year division was supposed to be robust with respect to the multivariate regression analyses.

13.2 Discussion of results

13.2.1 Lung cancer

Previous papers have documented an increased lung cancer incidence among workers in the SiC industry (SIR 1.9 (Romundstad), and SMR 1.7 (Infante-Rivard)). Our results were in accordance with these previous papers, with an overall lung cancer SIR of 2.0 (Paper I). However, our strengths in comparison with the previous investigations were on one hand 9 to 12 extra years of follow-up (Paper I and III), and on the other hand a comprehensive historical JEM (Paper III). We therefore had the possibility to plunge even deeper into the associations between several occupational circumstances and exposure factors, and lung cancer incidence. As crystalline silica and SiC fibers have been the exposure factors previously suspected of being the cause of the excess lung cancer, it has also been expected that the increase would be connected with work in the furnace hall, where the main exposures to both crystalline silica and fibers occur. Our findings were in accordance with this expectation. The lung cancer incidence among long term workers in the furnace hall was significantly increased compared to the general population (SIR 2.3), whereas the incidences in other departments were not significantly increased.

In table 3 and 4 in Paper III we found that all exposure factors showed an exposure-response association to lung cancer incidence when we used tertiles of cumulative exposure in both SIR and internal analyses, and even stronger associations were shown when exposure was lagged 20 years. The highest SIR and IRR, and the most significant trend, at highest exposure level and 20 years lag, was found for cristobalite, but other exposure factors also showed significant trends. These tables clearly show that exposure factors in the SiC industry were highly correlated, in the respect that high levels of exposure to one factor often indicated high exposures to other factors. This was especially the case in the furnace hall. However, the detailed JEM available in this study made it possible to differentiate further between exposures in the different job groups, and by log-transforming the

cumulative exposure and performing Poisson regression with continuous exposure variables a clearer pattern appeared, where crystalline silica in the form of cristobalite acted as a "confounder" in the analyses of all the other exposure factors, diminishing the effect estimate of SiC, and reducing the effect estimate of fibers, whereas adding other exposure factors to the cristobalite model had limited effect. Fibers, on the other hand, seemed to have some residual effect that did not disappear totally when other exposure factors were added to the Poisson model.

We find these results interesting, in the light of the discussions that still are lively after the 1997 IARC decision to classify crystalline silica as a Group I carcinogen (Carcinogenic to humans) (IARC, 1997). One of the suggestions following this decision was that the increase in lung cancer seen in some silica exposed cohorts was primarily due to cristobalite exposure from heating processes (McDonald and Cherry, 1999). Our findings were in accordance with this view, as we found that – at least the relatively low levels of – quartz exposure in the SiC industry seemed to have no effect on lung cancer incidence, whereas cristobalite had a profound effect.

The AM of cumulative exposure to cristobalite in the highest tertile was 0.3 mg*years/m^3 (range 0.09-2.7 mg x years/m^3), and the highest intensity of cristobalite exposure in the JEM was 0.23 mg/m^3. Rice (Rice et al., 2001) used the results from the Californian diatomaceous industry to estimate the lifetime excess risk of a worker exposed for 45 years to the Occupational Safety and Health Association standard of 0.05 mg/m^3 (= cumulative exposure 2.25 mg*years/m^3) to be 1.9 (95% CI 0.5-4.6). We found an SIR of 2.2 in the highest tertile of cristobalite cumulative exposure at a substantially lower cumulative exposure level.

In our multivariate analyses (Paper III, table 5) we found that some association between cumulative exposure to SiC fibers and lung cancer risk still remained after adjusting for other exposure factors. The fiber exposure levels in this study (AM 0.3-0.6 fibres/cm^3 in the furnace hall – Paper III) were higher than the current OEL for asbestos (0.1 fibres/cm^3 in Norway and many other countries). The median cumulative exposure to fibers in the highest cumulative exposure tertile was 3.9 fiber*years/cm^3 (range 2-93 fiber*years/cm^3), and the highest intensity of fiber exposure in the JEM was estimated to be 6.6 fibers/cm^3. No previous papers have reported SiC fiber exposure levels related to lung cancer incidence. In the Helsinki criteria for assessment of the relation between asbestos fiber exposure and lung cancer (Tossavainen, 1997), a cumulative dose of 25

fiber*years/cm^3 (fiber-years) were assumed to be a sufficient asbestos dose to induce lung cancer.

Although SiC fibers have shown characteristics similar to asbestos in toxicological studies and both asbestos and SiC fibers contain fibers with the highest toxicity according to the Stanton criteria of length > 8 µm and diameter < 0.25 µm (Skogstad et al., 2006; Stanton et al., 1981), the fibers are different in several aspects. Asbestos fibers are very thin, and split along the length direction, whereas SiC fibers are thicker and longer (Skogstad et al., 2006), and do not split, but break easily and become shorter. Thin fibers are not detected by the microscopical method used for fiber counting in this study as well as in most epidemiological studies of asbestos exposed workers. Thus, the asbestos exposure estimates that form the basis of the OELs are substantially more underestimated than the SiC fiber measurements in this study. Accordingly, assuming equal toxicity on a fiber basis, the SiC fiber exposure levels may not have been sufficient to contribute to the increased lung cancer risk in the present study to the extent that would be expected from the toxicological studies.

13.2.2 OLD

In accordance with other studies (Osterman et al., 1989b; Romundstad et al., 2002) we have observed an increased mortality from obstructive lung diseases and an increased reduction of lung function related to exposures in the SiC industry.

In addition to the observed increased mortality from OLD connected with affiliation to the furnace hall, we also, perhaps more surprising, found a somewhat weaker, but still significant, association between employment in the processing department, where SiC dust is the main exposure factor, and later death from OLD (Paper II). Analyses with specific exposure factors showed associations with cumulative exposure to SiC dust, both in analyses with tertiles of exposure to SiC, and in the multivariate analyses with adjustment for other ”confounding” exposure factors. This effect of SiC was observed among workers leaving the industry before they had been employed 15 years, but was not seen among the workers with more than 15 years of employment. Some studies have indicated that SiC exposure may increase the effect of other infectious or fibrogenic agents (Engelbrecht and Thiart, 1972; Gardner, 1923). Even though SiC in more recent toxicological studies not have shown cytotoxic and carcinogenic potentials (Bruch et al., 1993a; Bruch et al., 1993b), we cannot exclude a possible irritative or inflammatory reaction that at least among susceptible individuals may give symptoms and respiratory health problems. Because of the

amounts of SiC dust in the working environment this potential reaction would be expected to arise in the first years of employment.

Among workers employed > 15 years we observed an association between cumulative exposure to cristobalite and OLD mortality (Paper II). This association, however, was shown to be vulnerable to changes in the JEM, and high correlations with other exposure factors made it difficult to separate the effects of the specific factors. Analyses with the revised JEM showed similar effects from fiber exposure as from cristobalite exposure.

Reduced lung function is in many studies associated with exposure to dust (Marine et al., 1988; Ulvestad et al., 2001), but in most studies the dust has not been characterized into specific exposure factors. This is also the case in our lung function study, where an association between exposure to total dust and fall in FEV_1 per year is observed (Paper IV). It is, however, also of interest to examine the relations between lung function and specific dust factors, and we hope to be able to do this in the further follow-up of the study.

13.2.3 Other cancers and causes of death

We observed other cancers and causes of death in our study, which we only briefly discussed. Some of these findings it would be interesting to study more thoroughly. An increased incidence of stomach cancer was observed both by Infante-Rivard et al. and by Romundstad et al. (Infante-Rivard et al., 1994; Romundstad et al., 2001). Also in the first Norwegian cancer incidence report (Andersen 1980 – see page 25) a significantly increased SIR of stomach cancer was observed. In Paper I we observed non-significantly increased stomach cancer SIRs both among short- and long-term workers. Even though no additional stomach cancer cases were observed between 1996 and 2005, and only weak associations with work environment was found (Romundstad et al., 2001) a further study of stomach cancer in relation to specific occupational exposure factors could be of interest.

Increased incidences of cancers in lip and skin have also been consistent findings in the Norwegian SiC industry cancer studies (Romundstad et al., 2001) (Paper I), and as these cancer sites primarily have been associated with outdoor work, it would be interesting to examine if associations with specific dust factors in the SiC industry exist.

Both among short- and long-term workers an increased incidence of cancers in oral cavity and pharynx (OCP) were observed (Paper I). The most important risk factors for OCP cancers are tobacco and alcohol (Mayne et al., 2006). Both factors separately elevate the risk of OCP cancer, while tobacco and alcohol use together seem to act synergistically.

Several studies have examined the role of occupation in the etiology of OCP cancers, and excess risk has been observed among blue-collar workers with exposure to dust, inhaled organic agents, or inhaled inorganic agents (Maier et al., 1990). Among the long-term workers there was an increased incidence of OCP cancers, but no excess of other smoking and life-style associated cancers. A further study of these cancers related to dust factors in the SiC industry could possibly add to the knowledge about these cancers.

In addition, there was an increased incidence of leukaemia among long-term workers, and of Hodgkin's lymphoma and thyroid cancer among short-term workers (Paper I). The diversity among the cancer types and subtypes argues against a common cause. On the other hand, our knowledge about occupational risk factors for many cancers is limited, and we should be careful not to draw hasty conclusions.

Both among long-term workers and short-term workers an increased mortality from external factors was observed (Paper II). A closer study of the diagnostic codes showed that only one of the incidences was coded as a work accident.

Pneumonia as a cause of death was discussed in Paper II, and no indication of work relatedness was found. On the contrary, the high mortality from a disease associated with high age could in fact be interpreted as a healthy survivor effect.

14 Conclusions

Based on the results from these studies among workers in the Norwegian SiC industry the following conclusions may be drawn.

- We have confirmed the results from previous studies that workers in the Norwegian SiC industry have an increased incidence of lung cancer compared to the general population. These workers also have an excess mortality from obstructive lung diseases, like asthma, chronic bronchitis, COPD, and emphysema.
- The increased lung cancer incidence was mainly associated with work in the furnace hall. Exposure to cristobalite seemed to be the most important occupational risk factor, but an additional effect from exposure to SiC fibers could not be excluded. Smoking was the most important non-occupational risk factor.
- Mortality from obstructive lung diseases was mainly associated with work in the furnace hall, but also with work in the processing department. A high total dust exposure, with SiC particles as an important fraction, seemed to be the occupational exposure factors of greatest importance. We observed an effect of long term exposure to cristobalite, but these results were somewhat unstable and vulnerable to minor adjustments of the exposure data. Smoking was an important non-occupational risk factor.
- Workers with less than three years total duration of employment in the industry had a higher incidence of lung cancer and mortality from OLD than workers with longer employment duration. The lung cancer incidence was highest among workers employed in the first years of production, but a statistical significant increase was observed in all periods of first employment until 1980. After 1980, no increase was observed. Twenty years lag of exposure gave an increased exposure response association between most investigated exposure factors and lung cancer.
- An increased annual decrease in lung function, measured by FEV_1, was associated with increasing exposure to total dust. The effect was observed both among smokers and non-smokers.
- In addition, we observed an increased incidence of lip cancer and leukemia among long-term workers, and among short-term workers we observed increased incidences of non-melanoma skin cancer, thyroid cancer, Hodgkin's lymphoma, and cancer at unspecified sites. Excess mortality from other respiratory diseases as

pneumoconiosis and pneumonia, in addition to mortality from external factors was observed among long-term workers, and short term workers had an increased mortality from cerebrovascular diseases and external factors.

15 Current risk of lung diseases in the SiC industry

Only a few lung cancer cases were observed among workers with first employment after 1980, and the risk was not increased compared to the general population. It is, however, to early at this point in time to conclude whether the lung cancer risk in the Norwegian SiC industry is actually reduced to the level of the general population. Further follow-ups will be necessary in the coming years to conclude if the exposure-reducing measures have had the desired effect.

We have observed an increased mortality from obstructive lung diseases related to dust exposure, and we have also shown that dust exposures in the industry measured one decade ago was associated with reduced lung function. The increased risk of obstructive lung disease also during recent years is still very relevant for workers in the industry, where exposure to high levels of dust in combination with smoking adds to the risk.

16 Future research and recommendations

16.1 Future research

There is a need for further follow-up of both lung cancer incidence and OLD mortality in the Norwegian SiC industry, in order to evaluate the long term effects of exposure reducing measures. Further studies of lung function parameters related to exposure to specific dust factors are also of interest. Other cancer sites, together with other causes of death might also be addressed.

16.2 Prevention of lung diseases among workers

Further dust reduction is essential, not only in the furnace halls, where most of the exposure reducing measures up to now have been implemented, but also in the processing department, where high levels of total dust, specifically SiC particles, may induce lung function reduction and obstructive lung diseases. Another important measure to reduce the risk of lung diseases is, however, now as before, to reduce smoking.

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Original article

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Cancer incidence among short- and long-term workers in the Norwegian silicon carbide industry

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Bugge MD, Kjuus H, Martinsen JI, Kjærheim K. Cancer incidence among short- and long-term workers in the Norwegian silicon carbide industry. *Scand J Work Environ Health.* 2010;36(1):71–79.

Objectives A previous study among workers in the Norwegian silicon carbide industry, followed until 1996, revealed an excess incidence of lung and total cancer. The present study adds nine years of follow-up and focuses on cancer risk among short- and long-term workers, based on the assumption that these two groups have different exposure and lifestyle characteristics.

Methods The total cohort for this study comprised 2612 men employed for >6 months between 1913–2003. The follow-up period for cancer was 1953–2005. Short-term workers were defined as having <3 years of total employment in the industry. We estimated standardized incidence ratios (SIR) using national rates as the expected values.

Results Among the short-term workers, we observed an overall excess incidence of cancer [SIR 1.4, 95% confidence interval (95% CI) 1.2–1.6], with an excess of lung cancer (SIR 2.6, 95% CI 1.9–3.5) as the most important contributing factor. The long-term workers also had an excess incidence of total cancer (SIR 1.2, 95% CI 1.1–1.3) and lung cancer (SIR 1.7, 95% CI 1.3–2.2). We observed an increased risk of cancers at other sites, specifically among short-term workers.

Conclusions We observed an increased risk of cancer (especially in the lung but also at other sites) among both short- and long-term workers. Dust exposure in the silicon carbide industry may have contributed to the increased risk among long-term workers, whereas the increased risk among short-term workers may be due to a combination of occupational and lifestyle factors.

Key terms dust exposure; epidemiology; lung neoplasm; lung; neoplasm; smoking.

Crystalline silica (quartz and cristobalite) and silicon carbide (SiC) particles and fibers are the main constituents of the dust found in the SiC industry's working atmosphere (1, 2). In vitro and animal studies have shown SiC fibers to be highly toxic and comparable to crocidolite asbestos with regard to carcinogenic potential (3–7). The SiC industry's working environment may also be polluted by carbon monoxide, sulphur dioxide, and small amounts of volatile polycyclic aromatic hydrocarbons (PAH) (8, 9).

Since around the 1920s, possible health risks related to the production of SiC have been discussed. In 1919, Winslow et al (10) reported an increased risk of tuberculosis among SiC workers and commented: "We have every reason to expect … that dusts of this nature should be exceedingly deleterious to health." The first published study on cancer risk among SiC workers (11) showed an increased mortality from cancer of the lung [standardized mortality ratio (SMR) 1.69, 95% confidence intervals (95% CI) 1.09–2.52] and stomach cancer (SMR 2.18, 95% CI 0.88–4.51). More recently, the Norwegian Cancer Registry performed a cancer incidence study among 2620 SiC workers in three Norwegian plants (12). The study reported an overall increased cancer risk [standardized incidence ratio (SIR) 1.2, 95% CI 1.1–1.3], mainly due to increased risk of lung cancer (SIR 1.9, 95% CI 1.5–2.3). In addition, the study found an increased risk of cancer of the stomach (SIR 1.5, 95% CI 1.1–2.0) and the upper respiratory tract (SIR 1.7, 95% CI 1.0–2.7), together with a borderline increased risk of lip cancer (SIR 2.0, 95% CI

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0.9–3.9) and non-melanoma skin cancer (SIR 1.5, 95% CI 0.9–2.5).

These are the only two published epidemiologic studies of cancer risk among workers in the SiC industry. Both addressed lung cancer in relation to cumulative exposure to total dust and indicated an exposure–response relationship between lung cancer incidence and cumulative dust exposure. However, the Canadian study (11) was very small (N=585), and – even if the SMR of lung cancer showed increasing risk estimates with increasing exposure – the power of the study was too weak to give statistically significant results (11). In the Norwegian study (12), the non-exposed group had a risk of 0.6 of the expected number, whereas the SIR increased to 1.9 in the group at the lowest level of exposure, flattened out, and showed only a limited increase with increasing exposure levels. The authors suggested that the approximate nature of the exposure estimates and chance may have led to errors that easily could have biased the shape of the exposure–response relation.

Previous studies in different industries have found divergent cancer risk patterns between short- and long-term workers with the former having the highest risk (eg, of lung cancer) (13, 14). It has been suggested that this may be due to, on the one hand, exposure characteristics (eg, short-term workers have a tendency to get jobs with the heaviest dust exposure) and, on the other hand, lifestyle factors (eg, short-term workers are heavier smokers than long-term workers) (15–17).

The previous Norwegian Cancer Registry study comprised 74 lung cancer cases. In the present study, nine more years of observation have been conducted (1997–2005). Our aim was to examine cancer incidence, especially that of lung cancer, in relation to (i) duration of employment, (ii) period of first employment, and (iii) time since first employment. We specifically addressed cancer incidence among short- and long-term workers, respectively.

Methods

Study population

The study population is based on the earlier SiC cohort (12). The cohort was established on the basis of personnel registers at three Norwegian plants, comprising altogether 2720 men. With the omission of 40 workers, who died before 1953, and 60 unidentifiable individuals, the previous follow-up included 2620 men with a working history of >6 months in the SiC industry (12).

In our study, the cohort (see table 1) was extended with employment histories and new employees from the period 1997–2003 (N=130 men). One double registration in the old cohort was removed, and three formerly unidentifiable persons omitted from the old cohort were identified and added to the present cohort.

Following a request from the Norwegian Data Inspectorate, we sent an information letter to all registrants still living, giving them the opportunity to refuse participation in the follow-up study. Altogether, 121 persons refused participation, which left us with a study cohort of 2631 men employed in the SiC industry for a total of ≥6 months, and first employed at one of the three plants between 1913 and 2003. The regional Ethics Committee endorsed the study.

Employment records were the main source of individual information on employment. We recorded the employee's name, date of birth, and/or the unique 11-digit identification number (established in 1964, and given to all Norwegians alive in 1960 or born later) and, where available, up to 11 employment periods with location of work and work tasks. When available, we obtained the individual's smoking history from the occupational health services at the plants. Through linkage via the 11-digit ID number, cancer diagnoses and dates of death and emigration were obtained from the Cancer Registry of Norway. For employees deceased before

Table 1. Some characteristics of the cohort of 2612 workers in the Norwegian silicon carbide industry.

	Total cohort (N=2612)				Short-term workers (N=925)				Long-term workers (N=1687)			
	N	%	Median	5th–95th percentile	N	%	Median	5th–95th percentile	N	%	Median	5th–95th percentile
Year at start of first employment	–	·	1968	1932–1996	–	·	1966	1936–2001	–	·	1969	1928–1995
Age at start of first employment	–	·	27.9	17.1–54.9	–	·	26.5	16.5–53.7	–	·	28.8	17.7–55.3
Duration of total employment (years)	–	·	6.1	0.7–35.3	–	·	1.25	0.6–2.7	–	·	14.8	3.4–37.5
Year at death	–	·	1988	1962–2004	–	·	1986	1961–2004	–	·	1989	1962–2004
Duration of follow-up (years)	–	·	24.1	3.7–45.5	–	·	25.5	2.0–47.2	–	·	23.6	5.0–44.7
Person-years of observation 1953–2005	63 407	100	·	·	22 998	36	·	·	40 409	64	·	·

1960, Cancer Registry data were obtained through linkage with the individual's name and date of birth. After linkage, we made the database anonymous. The variables for further analyses were: (i) year and month of birth, (ii) up to four cancer diagnoses with year and month of diagnosis, (iii) diagnostic code, (iv) histology or morphology code, (v) year and month of death or emigration, (vi) and employment information. For 2067 persons (78.6%), we also had information on whether they had ever been smokers.

Follow-up and analysis of cancer incidence

We defined long-term employees as workers with >3 years of total employment in the SiC industry. The follow-up of cancer incidence among long-term workers started after 3 years duration of employment or from 1 January 1953 (when the Cancer Registry was established), if the 3 years duration of employment was reached earlier.

The follow-up of short-term workers started one year after the end of last employment in the SiC industry or from 1 January 1953 in order to exclude short-term workers quitting because of disease or death. Before the start of follow-up, 19 short-term workers died or emigrated, reducing the cohort to 2612 workers. For analyses of lung cancer incidence, the end of follow-up was the date of lung cancer diagnosis, date of death or emigration, or the end date of study (ie, 31 December 2005). For the study of total cancer, the end of follow-up was the date of death or emigration or the end date of study. Table 1 shows the distribution of person-years for the follow-up of total cancer. For the follow-up of lung cancer, a total of 63 197 person-years was accumulated (data not shown). Among the lung cancer cases, one subject had two primary diagnoses of lung cancer.

Through the Cancer Registry of Norway, we had access to cancer diagnoses in the population for all sites and types of cancer except basal cell carcinoma, which is not included in the present study. Pathology laboratories and clinical departments compulsory reporting of cancer ensures a complete register (18). During the entire follow-up period, cancer diagnoses classified according to a modified version of the World Health Organization's International Classification of Diseases (ICD-7) were available. We calculated the expected numbers of cancer cases in the cohort on the basis of national incidence rates for 5-year calendar periods and age groups. We used the national incidence rates of all cancers, except basal cell carcinoma, for the analyses of total cancer. For the analyses of lung cancer, the national incidence rates of lung cancer were used. We computed the SIR as the ratio between the observed and expected number. Assuming a Poisson distribution of the observed numbers, we calculated 95% CI using Stata software (StataCorp LP, College Station, TX, USA). We analyzed the possible effects of (i) duration of employment, (ii) period of first employment, and (iii) time since first employment; the analyses were performed separately for the two sub-cohorts of short- and long-term workers. To investigate the effect of smoking on lung cancer, we performed incidence analyses stratified by never-/ever-smokers.

Results

Altogether, we observed 531 cancer cases among the 2612 workers in the total cohort, compared to the expected number of 424.9, which gives a SIR of 1.3 (95% CI 1.1–1.4). The most important single cancer site contributing to the observed excess was an increased lung cancer incidence with 103 cases versus the 51.7 expected (SIR 2.0, 95% CI 1.6–2.4).

Table 2 shows the SIR of all cancers for short- and long-term workers, respectively. In both groups, the SIR of total cancer were increased. Short-term employees had a SIR of 1.4 (95% CI 1.2–1.6), and long-term employees had a SIR of 1.2 (95% CI 1.1–1.3). Elevations were also seen for lung cancer and cancers of the oral cavity and pharynx (OCP). For lung cancer, we observed SIR of 2.6 and 1.7 among the short- and long-term workers, respectively.

The short-term workers also had increased incidence of non-melanoma skin cancer, thyroid cancer, Hodgkin's lymphoma, and cancer at unspecified sites. Elevated SIR levels, although non-significant, were seen for several others cancers sites, such as lip, esophagus, stomach, liver, pleura, and bladder. In the long-term worker group, there was an increased incidence of lip cancer and leukemia, in addition to a borderline increased incidence of prostate cancer. We also observed non-significant excesses of cancers of the stomach, nose, and skin.

By separating lung cancers into subgroups by histological type, we found that the group "other and unspecified lung cancer" contained the major part of the lung cancer cases and was significantly increased among both short- (24 cases, SIR 4.4, 95% CI 3.0–6.6) and long-term workers (28 cases, SIR 2.4, 95% CI 1.7–3.5). There was a significant increase of small-cell cancer among the short-term workers and squamous-cell cancer among long-term workers. Adenocarcinoma was non-significantly increased in both groups (data not shown).

Table 3 shows the SIR for lung cancer related to the duration of employment. These were significantly elevated for those with ≤5 years of employment. For longer employment durations, risk estimates were somewhat lower but still above unity.

Among short-term workers, the risk estimates for the group "cancer, all sites except lung" were higher

for those first employed in the more recent time periods (table 4), whereas the long-term workers had fairly stable, slightly elevated SIR irrespective of the period of first employment. In both sub-cohorts, lung cancer risk was significantly elevated in all periods of first employment except for workers employed after 1980, where only one lung cancer case was observed. The SIR for lung cancer was highest among those employed in the earlier periods, in particular among the short-term workers.

The analyses stratified by time since first employment (table 5) showed an increased lung cancer incidence ≥20 years after first employment, among both short- and long-term workers. Among the latter, the SIR were the same regardless as to whether workers had been employed less or more than 10 years.

We also performed analyses of lung cancer stratified by smoking status (table 6). No lung cancer cases occurred among never-smoking, short-term workers, and there was only one case among never-smoking, long-term workers.

Table 2. Observed (Obs) number of cases and standardized incidence ratio (SIR) of cancer, all sites, with 95% confidence interval (95% CI), 1953–2005, among 2612 male Norwegian silicon carbide short- and long-term workers employed >6 months 1913–2003. [ICD-7= International Classification of Diseases, 7th revision].

Site (ICD-7 code)	Short-term workers (N=925)			Long-term workers (N=1687)		
	Obs	SIR	95%CI	Obs	SIR	95%CI
Lip (140)	3	2.1	0.7–6.7	7	2.4	1.2–5.1
Oral cavity, pharynx (141, 143–148)	6	2.5	1.1–5.6	10	2.1	1.1–3.9
Digestive organs (150–159)	37	1.0	0.8–1.4	82	1.1	0.9–1.3
Esophagus (150)	3	1.9	0.6–5.8	3	0.9	0.3–2.7
Stomach (151)	13	1.4	0.8–2.4	25	1.3	0.9–1.9
Small intestine (152)	0	0.0	0.0–8.0	2	2.1	0.5–8.3
Colon (153)	11	1.0	0.5–1.8	26	1.0	0.7–1.5
Rectum (154)	3	0.4	0.1–1.3	15	1.0	0.6–1.7
Liver (155)	2	2.3	0.6–9.1	2	1.1	0.3–4.2
Pancreas (157)	5	1.2	0.5–2.8	9	1.0	0.5–1.9
Nose, sinuses, etc (160)	0	0.0	0.0–9.7	2	2.6	0.6–10.4
Larynx (161)	2	1.3	0.3–5.1	3	0.9	0.3–2.8
Trachea, bronchus, and lung (162)	43	2.6	1.9–3.5	60	1.7	1.3–2.2
Pleura (163)	2	3.7	0.9–14.7	1	0.8	0.1–6.0
Prostate (177)	26	0.9	0.6–1.3	77	1.2	1.0–1.5
Testis (178)	1	0.5	0.1–3.9	2	0.6	0.2–2.4
Kidney, ureter (180)	4	0.8	0.3–2.2	10	1.0	0.5–1.9
Bladder and other urinary organs (181)	13	1.4	0.8–2.4	19	0.9	0.6–1.5
Melanoma of skin (190)	6	1.2	0.5–2.7	15	1.5	0.9–2.5
Other skin (non-melanoma) [a] (191)	11	2.1	1.1–3.7	18	1.5	0.9–2.3
Brain, nervous system (193)	3	0.8	0.3–2.5	5	0.7	0.3–1.7
Thyroid gland (194)	4	5.8	2.2–15.4	1	0.7	0.1–5.2
Hodgkin lymphoma (201)	4	5.2	2.0–13.9	1	0.7	0.1–5.1
Non-Hodgkin lymphoma (200 + 202)	1	0.3	0.0–2.3	8	1.2	0.6–2.4
Multiple myeloma (203)	4	1.8	0.7–4.7	3	0.6	0.2–1.9
Leukemia (204)	2	1.8	0.5–7.4	6	2.8	1.2–6.1
Unspecified sites (199)	10	2.1	1.2–4.0	11	1.1	0.6–2.0
Other specified sites	2	0.8	0.2–3.4	6	1.3	0.6–2.8
All sites (140–204)	184	1.4	1.2–1.6	347	1.2	1.1–1.3

[a] Except basal cell carcinoma.

Discussion

In the present study, we observed an increased risk of lung cancer among workers in the Norwegian SiC industry, among both short- and long-term workers. Lung cancer risk was specifically elevated among workers with <5 or >20 years of employment and those with first employment in earlier periods. In addition to lung cancer, we observed an increased risk of other types of cancer among both short- and long-term workers.

The cohort

In this study, we had access to a large cohort of more than 2600 workers, with the first employments dating back almost 100 years and a follow-up time of >50 years. The Cancer Registry of Norway claims a high level of completeness of cancer diagnoses, and the Norwegian unique 11-digit identification number ensures correct linkage between databases.

Workers in the cohort were employed at two smelters located in the southern region of Norway and one in the mid-region of the country. Since the incidence of lung cancer varies in the different regions of Norway,

Table 3. Observed number of cases (Obs), and standardized incidence ratio (SIR) of lung cancer, with 95% confidence interval (95% CI), 1953–2005, among 2612 male Norwegian silicon carbide workers employed >6 months 1913–2003, by duration of employment.

Duration of employment	Person-years	Obs	SIR	95% CI
Short-term workers				
0.5–0.9 years	8406	12	2.0	1.1–3.5
1–1.9 years	9886	21	3.0	1.9–4.5
2–2.9 years	4656	10	3.1	1.7–5.8
Long-term workers				
3–4.9 years	7958	12	2.2	1.3–3.9
5–9.9 years	10 438	10	1.5	0.8–2.8
10–19.9 years	11 890	13	1.4	0.8–2.4
≥20 years	9963	24	1.8	1.2–2.7

use of regional rates might give somewhat different results. When substituting the national rates for lung cancer with the rates for the region that contributed the largest number of cases, we found that the SIR of lung cancer was reduced from 2.0 (95% CI 1.6–2.4) to 1.7 (95% CI 1.4–2.0), which was still a significant increase. The SIR levels were still significantly increased when dividing the cohort into short- and long-term workers, using these regional rates. We chose to use the national incidence rates for the calculation of expected values due to their robustness.

In the present study, cohort members still living were given the opportunity to refuse participation, and 121 of 1477 individuals did so. If refusal is outcome dependent, a possible bias is introduced. We have no information as to the reasons for non-participation. Comparing the non-participants with the participating, living members of the cohort, we found that the non-participants were older, had their first employments in earlier time periods, and had a shorter duration of employment. We have no reason to believe that workers who already had been diagnosed with cancer, systematically declined

Table 4. Observed (Obs) number of cases, and standardized incidence ratio (SIR) of cancer, with 95% confidence interval (95% CI), 1953–2005, among 2612 male Norwegian silicon carbide short- and long-term workers employed >6 months 1913–2003, by period of first employment.

Period of first employment	Short-term workers				Long-term workers			
	N	Obs	SIR	95% CI	N	Obs	SIR	95% CI
Cancer, all sites except lung								
1913–1939	69	10	0.7	0.4–1.2	184	54	1.2	0.9–1.6
1940–1959	280	73	1.3	1.0–1.6	294	76	1.0	0.8–1.2
1960–1979	389	51	1.4	1.0–1.8	772	143	1.4	1.2–1.6
1980–2003	187	7	3.5	1.7–7.4	437	14	1.8	1.0–3.0
Lung cancer								
1913–1939	69	6	3.7	1.6–8.2	184	10	2.1	1.1–3.9
1940–1959	280	23	2.7	1.8–4.1	294	24	2.1	1.4–3.2
1960–1979	389	14	2.6	1.5–4.3	772	25	1.7	1.1–2.5
1980–2003	187	0	0.0	0.00–16.8	437	1	1.0	0.1–6.8

Table 5. Observed (Obs) number of cases, and standardized incidence ratio (SIR) of lung cancer, with 95% confidence interval (95% CI), 1953–2005, among 2612 male Norwegian silicon carbide short- and long-term workers employed >6 months 1913–2003, by time since first employment and employment duration.

Employment duration	Time since first employment							
	<20 years				≥20 years			
	Person-years	Obs	SIR	95% CI	Person-years	Obs	SIR	95% CI
Short-term workers	11 296	2	0.70	0.2–2.8	11 652	41	3.04	2.2–4.1
3–9.9 years	12 890	8	1.78	0.9–3.6	5 511	14	1.87	1.1–3.2
≥10 years	8 094	2	0.53	0.1–2.1	13 760	35	1.86	1.3–2.6

Table 6. Observed (Obs) number of cases, and standardized incidence ratio (SIR) of lung cancer, with 95% confidence interval (95% CI), 1953–2005, among 2631 male Norwegian silicon carbide short- and long-term workers employed >6 months 1913–2003, by smoking status.

Smoking status	Short-term workers					Long-term workers				
	N	%	Obs	SIR	95% CI	N	%	Obs	SIR	95% CI
Ever-smokers	362	39.1	22	3.3	2.2–5.0	1165	69.1	55	2.3	1.7–3.0
Never-smokers	166	17.9	0	0	0.0–2.3	359	21.3	1	0.1	0.0–0.9
Unknown smoking status	397	42.9	21	2.6	1.7–4.0	163	9.7	3	1.1	0.4–3.6

participation in the study. Thus, a possible systematic selection out of the cohort would most probably lead to a differential loss of healthy workers, which could have resulted in somewhat inflated SIR estimates. To further explore this possibility, we analyzed the SIR of lung cancer with follow-up ending in 1996 and compared the results with that of the previous cohort follow-up (12), removing those who declined participation in the present cohort. We found similar SIR between the two cohorts, indicating that non-participation of <5% of the cohort had not introduced any selection bias of importance. In a further sensitivity analysis with follow-up to 2005, in adding the employment periods of the individuals who declined inclusion (assuming none had developed cancer), we observed a slight reduction in the observed SIR, but the associations were still statistically significant, both in the total cohort (SIR of lung cancer 1.9, 95% CI 1.5–2.3, compared with SIR 2.0, 95% CI 1.6–2.4 in the present study), and in the sub-cohorts of short- and long-term workers. We, therefore, presume that our results are valid with respect to selection bias from this source.

Comparing results with earlier studies

Two previous cohort studies among SiC workers have shown an increased risk of lung cancer in this industry (11, 12). Both studies concluded that the risk seemed to increase with higher levels of exposure, a criterion usually considered in favor of causality (19). In the present study, using employment duration as an indicator of exposure, we could not confirm a corresponding pattern between increasing SIR of lung cancer and the duration of exposure.

Both Infante-Rivard et al (11) and Romundstad et al (12) addressed stomach cancer in their papers on the SiC industry. In the Canadian study, the increased stomach cancer incidence was non-significant (7 cases, SIR 2.18, 95% CI 0.88–4.51). In the Norwegian study, the SIR of stomach cancer was 1.5 (95% CI 1.1–2.0), but the authors found only weak evidence for a causal association with the working environment. The overall SIR of stomach cancer in the present study was 1.3 (95% CI 1.0–1.8). No new stomach cancers were diagnosed during the additional nine years of follow-up time. Even though exposure to dust and silica are mentioned as suspected risk factors for stomach cancer (20), the most important etiologic factor for this cancer is infection by *Helicobacter pylori* (21). There was little indication that stomach cancer was associated with occupational factors in our study.

Romundstad et al (12) also observed borderline increases of lip and non-melanoma skin cancers. In our study, the incidence of lip cancer was increased among both long- and short-term workers, although non-significantly in the latter group. The incidence of non-melanoma skin cancer was non-significantly increased among long-term workers and significantly increased among short-term workers. Earlier studies have shown strong associations between lip cancer and smoking, especially in combination with outdoor work (exposure to sunshine) (22). Similarly, non-melanoma skin cancer is primarily associated with sunshine, although association with non-solar (including some occupational) exposures have been discussed, among them exposure to PAH (23). Previous measurements of PAH in the SiC industry have indicated low levels (9), but we cannot exclude that skin exposure to PAH may have contributed to the observed excess of non-melanoma skin cancer among the workers.

Lung cancer

Lung cancer risk was significantly elevated for workers employed in all periods since the first plant started in 1913, except for those employed in 1980 or later, where only one case of lung cancer was observed. The SIR seem to decrease by period of first employment, indicating that the lung cancer risk actually may be reduced in later years compared to the earliest years of production. On the other hand, the latency period for developing lung cancer is so long that most lung cancer cases caused by exposure in this last period would not yet be evident.

The analyses stratified by time since first employment showed an increased lung cancer incidence ≥20 years after first employment, among both short- and long-term workers. As in the other analyses, the SIR level of short-term workers was higher than that of long-term workers. Among long-term workers, stratifying employment duration in periods of <10 years and ≥10 years showed no difference between the groups. The increased SIR ≥20 years after first employment is in accordance with knowledge of the latency time for development of lung cancer, given exposure to relevant carcinogens in the SiC industry.

However, a high lung cancer risk with short employment duration indicates additional exposure to carcinogens outside the SiC industry. In addition to tobacco use, the finding of three pleural cancers, two of which are classified as mesotheliomas and the third as "malignant tumor, uncertain mesothelioma", indicates some asbestos exposure among the employees. All three smelters in question are located on the Norwegian coast, and we know that many seamen were recruited for employment, particularly in the oldest plant under study. There was also some exchange of workers between these plants and other polluted industries in the study regions, but we have no further information about previous or later jobs. Thus, apart from asbestos exposure in the SiC industry, exposure to asbestos from time spent in other

dusty industries or during machine room work on ships is likely to have occurred.

The smoking data available from the main part of the cohort were limited to "non-smokers", "smokers" and "ex-smokers". As we did not have information on duration of smoking and dates of quitting, the ex-smoker data were impossible to utilize in the time-dependent analyses. Altogether, 60% were registered as "ever smokers", 20% as "never smokers" and 20% as unknown smoking status. According to Axelson (24), the fraction of smokers in industrial populations seldom exceeds 70%. Using this estimate, he found that excess smoking among industrial workers relative to the general population could increase the incidence of lung cancer with a rate ratio of 1.43 (24). The SIR for lung cancer found in the present study were considerably higher than 1.43. Based on the same, sparse smoking data, Romundstad et al (12) found that the excess incidence of lung cancer in the previous Norwegian SiC cohort study did not seem to be confounded by smoking.

Short- and long-term workers

The highest SIR for lung cancer were seen among the short-term workers, and among the long-term workers the SIR were fairly stable with increasing employment duration. Ideally, for a causal association, one would have expected an increasing trend in risk with increasing duration of employment, but as employment duration is an imperfect exposure indicator, results should be interpreted with caution.

Several authors have addressed the fact that cancer incidence is often increased among short-term workers, and many occupational epidemiologic studies show increased cancer risk in this group only (13, 14). Only a few authors, however, have thoroughly studied short-term workers per se and tried to investigate the reasons why this group shows both a higher cancer incidence and a higher total mortality than long-term workers (15–17). Gubéran & Usel (15) found that the prevalence of smoking, exposure to asbestos, and occupational accidents in later work were higher among workers employed for <2 months in the Geneva perfumery industry than among a reference population. Lamm et al (16) reviewed past working histories in a cohort of 741 New York State tremolitic talc workers and concluded that an increase in lung cancer mortality among the short-term employed most likely was due to exposure elsewhere (prior employment, smoking, other factors). The authors argued that the inclusion of short-term employees in epidemiologic studies may sometimes have a magnifying effect on the association between work environment and risk, whereas the traditional argument for excluding short-term employees has been the risk of diluting the association. Stewart et al (17) performed an occupational hygiene study comparing the jobs, exposures, and mortality experience of workers employed ≤1 year to workers employed >1 year in formaldehyde plants. They showed that short-term workers had no greater exposure to formaldehyde, but that they were more likely to be in jobs exposed to particulates than long-term workers. The short-term workers had greater overall mortality risks than their long-term counterparts.

In this study, we have performed analyses stratified on short- and long-term employees, where the cut-off point, a priori, was set to three years, in accordance with the previous cohort study (25). Many authors have suggested that short-term workers should be treated as a special group, and that a study including both short- and long-term workers will give biased results (13, 14). This view is supported by the results from the present study, indicating that the short-term workers in fact may be a group with high risk of cancer, either from occupational exposure or from exposure to other risk factors. In our study, follow-up of the short-term workers started one year after the end of last employment, in order to minimize any effect of employment being terminated due to illness. During this period, 19 workers died or emigrated and were, consequently, excluded from the study.

In our study, we observed an excess of several cancers which are associated with lifestyle factors among short-term workers. In addition to lung cancer, which is associated with smoking, we found an excess of OCP cancers. The most important risk factors for OCP cancers are tobacco and alcohol (26). Both factors separately elevate the risk of OCP cancer, while tobacco and alcohol use together seem to act synergistically. Several studies have examined the role of occupation in the etiology of OCP cancers, and excess risk has been observed among blue-collar workers with exposure to dust, inhaled organic agents, or inhaled inorganic agents. There is little consistency to these findings, however, and it has been difficult to isolate occupational exposures from the effects of smoking and drinking (26). Also, we observed an excess of (i) lung cancer with no specific histological diagnosis ("other" lung cancers) and (ii) cancers at unspecified sites, both of which have been associated with low socioeconomic status (27). The risk of other smoking-related cancers (eg, cancers of the bladder, pancreas, and larynx) showed a non-significant increase. In the short-term worker group, we observed an excess incidence of thyroid cancer (SIR 5.8) and Hodgkin's lymphoma (SIR 5.2), both based on a small number (four cases each). Fillmore et al (28) reported an increased risk of thyroid cancer among women exposed to silica, but no such increased risk among men. We have not found any other evidence in support of associations between occupational exposures in the SiC industry and these types of cancer.

Moreover, there was an increased incidence of lung and OCP cancers among the long-term workers but no excess of other smoking and lifestyle-associated cancers. In addition to the already discussed lip, skin, and stomach cancers, there was increased incidence of leukemia. The subtypes showed great variation, with the six cases comprising two acute lymphatic leukemia, one chronic lymphatic leukemia, two chronic myelomonocyte leukemia, and one unspecified leukemia. This great diversity argues against a common cause.

Lifestyle factors, smoking in particular, could thus be the main reasons for the excess cancer incidence observed among short-term workers in this study. However, Gubéran & Usel (15) and Stewart et al (17) showed that short-term workers have a higher tendency to be employed in dusty and unhealthy jobs, indicating that work environmental factors may contribute to the excess lung cancer risk also among short-term workers. The results indicate that differential selection bias and confounding between short- and long-term workers may distort the assessment of exposure–response relationships in cohorts of occupationally exposed workers.

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II

III

Lung cancer incidence among Norwegian silicon carbide workers – associations with particulate exposure factors

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What this paper adds:

- Workers in the silicon carbide industry have increased incidence of lung cancer
- The specific causal factors of this increase have not previously been known
- The present study shows that exposure to cristobalite and silicon carbide fibers seem to be the most important occupational risk factors
- Control of the dust exposure in the silicon carbide industry, especially in the furnace hall, is essential

Abbreviations: CI, confidence interval; IARC, International agency for research on cancer; ID, identification; IRR, incidence rate ratio; JEM, job exposure matrix; LR-test, likelihood ratio test; *n*, number; PAH, polycyclic aromatic hydrocarbon; SiC, silicon carbide; SIR, standardized incidence ratio

ABSTRACT

Objectives: An increased lung cancer risk associated with total dust exposure in the silicon carbide (SiC) industry has previously been reported. The aim of the present study was to examine the relative importance of specific exposure factors, by using a comprehensive, historic job exposure matrix based on about 8,000 measurements.

Methods: Cumulative exposure to total and respirable dust, respirable quartz, cristobalite, and SiC particles, and SiC fibers, was assessed for 1,687 long-term workers employed 1913-2003 in the Norwegian SiC industry. Standardized incidence ratios (SIR) for lung cancer, with follow-up 1953-2008, were calculated stratified by cumulative exposure categories. Poisson regression analyses were performed using both categorized and log-transformed cumulative exposure variables.

Results: The lung cancer incidence was about two-fold increased at the highest level of exposure to each of the exposure factors (SIR 1.9-2.3 for all agents). Internal analyses showed associations between exposure level and lung cancer incidence for all investigated factors, but a significant trend only for total dust and cristobalite. In multivariate analyses cristobalite showed the most consistent associations, followed by SiC fibers.

Conclusions: The results indicated that crystalline silica in the form of cristobalite was the most important occupational exposure factor responsible for lung cancer excess in the Norwegian SiC industry. SiC fibers seemed to have an additional effect.

Previous studies have shown that workers in the silicon carbide (SiC) industry have an increased risk of lung cancer. In a Canadian study the standardized mortality ratio of lung cancer was 1.7 (95% confidence interval (CI): 1.1, 2.5)[1]. Cancer incidence among Norwegian silicon carbide workers is previously studied in two follow-ups, with end-points 1996 and 2005, with standardized incidence ratios (SIR) of lung cancer 1.9 (95% CI: 1.5, 2.3) and 2.0 (95% CI: 1.6, 2.4)[2, 3], respectively. Exposure-response associations were found with exposure to total dust, but due to limited information about exposure to specific dust components further studies with more detailed job exposure information were recommended[1, 3].

Several airborne exposure factors in the SiC production are known or suspected lung cancer risk factors. Quartz and cristobalite, two polymorphs of crystalline silica, are both classified as carcinogenic to humans (International agency for research on cancer (IARC) - class 1)[4]. *In vivo* and *in vitro* studies have indicated that SiC fibers have toxicological similarities to asbestos fibers, which are known lung carcinogens[5]. On the other hand, the most abundant exposure factor in the SiC industry, isometric SiC particles, has not shown carcinogenic potential in *in vivo* or *in vitro* studies[6, 7].

The aim of this study was to examine the relative importance of the investigated exposure factors; quartz, cristobalite, SiC particles, and SiC fibers, with respect to lung cancer risk in the Norwegian SiC industry, by using a comprehensive, historic job exposure matrix (JEM).

The study was approved by the Regional Committee for Medical Research Ethics South-East Norway, and by the Norwegian Data Inspectorate.

MATERIALS AND METHODS

Study cohort

The study cohort was based on a previously established cohort in the Norwegian SiC industry[2, 3]. It consisted of 1,687 men, employed in 1942 and onwards, with ≥ 3 years employment in the Norwegian SiC industry between 1913 and 2003, and alive after 1 Jan 1953. The database comprised name, date of birth, the Norwegian unique 11-digit identification (ID)-number, plant affiliation, employment dates, job code(s), and smoking information, classified as never-/ever-smoker, and unknown. The cohort was linked with the Norwegian Cancer Registry to obtain cancer diagnoses and dates of diagnosis for the period 1 Jan 1953 to 31 Dec 2008, in addition to dates of death and emigration. Linkage was performed using the Norwegian unique 11-digit ID-number, assigned to all Norwegian citizens alive in 1960 or born later. Before 1960, linkage was performed manually, using name and date of birth. After linkage, name and ID-number was replaced by a unique, random number. Follow-up started after 3 years of total employment, or 1 January 1953, if the 3 years' duration of employment was reached earlier. End of follow-up was date of lung cancer diagnosis, date of death or emigration, or 31 December 2008. The 1,687 workers contributed 42,910 person-years of follow-up to the study.

Silicon carbide production

The production of silicon carbide by the Acheson method[8] was established in Norway in 1913. By this method, a mixture of quartz sand and petroleum coke is heated in open electric resistance furnaces by a graphite core. The heating process lasts approximately 48 hours, during which the temperature in the core approaches 2,500˚C. Quartz will react with carbon

and form SiC and carbon monoxide at temperatures above 1,720˚C. At the end of the heating process, SiC is found in the region closest to the core. Further away from the core partly reacted material is found, and in the periphery, where the temperature can reach 1,000˚C, no transformation takes place. SiC fibers are formed during the process[9] and are accumulated in the intermediate region, where the partly reacted material is found[10]. The unreacted and partly reacted material is removed from the crude before transport to the processing department where the SiC is crushed and sieved, impurities are removed, and the grains are classified into size fractions before packing. The petroleum coke contains impurities of sulfur, which is oxidized to sulfur dioxide during the furnace process, and traces of polycyclic aromatic hydrocarbons (PAH) in varying amounts. Cristobalite, a high temperature crystalline phase of silica, is formed during the furnace process, through transformation of quartz at around 1,500˚C.

Exposure assessment and job exposure matrix

Since 1967, personal total dust exposure has been measured with reference to specific job groups for routine control purposes and in connection with scientific exposure studies in the three Norwegian SiC plants. About 3,300 measurements of total dust were available for reconstruction of the historical exposure levels. Based on the available total dust measurements and information from the plant personnel about changes in production technology and working hours in earlier periods, estimates of exposure levels to total dust were modeled for all job groups and all years of production from 1913 to 2005.

In order to estimate exposure to specific agents, a large comparative study was performed in 2002-2003[11], with 600-700 parallel personal measurements of total dust and respirable dust,

and total dust and fibers. The amounts of quartz, cristobalite, and SiC dust in the respirable dust fraction were determined[11]. This comparative study added approximately 5,000 measurements to the exposure data. Based on the assumption, with a few exceptions, of a constant composition of the dust over time, exposure in each job group and year to each specific exposure factor was modeled from the historical total dust estimates, forming a job exposure matrix (JEM). A few historical measurements of PAH showed low levels compared to occupational exposure limits, and PAH was therefore not included in the comparative measurement study. Asbestos exposure was categorized as never-/ever-exposed, and linked to job groups that had probable asbestos exposure in relevant time periods. The development of the job exposure matrix is described in detail in Føreland et al. 2012[12]. Some characteristics of the cohort and mean levels of the exposure factors are summarized in table 1. Arithmetic means (AM) were estimated from geometric means (GM) and geometric standard deviations (GSD) as described by Seixas et al.[13], using the formula $AM=GM*\exp(0.5(\ln GSD)^2)$.

Cumulative exposure

The information about employment periods and job codes for each individual in the cohort enabled a linkage with the JEM, thereby assigning individual mean exposures to total dust, respirable dust, respirable quartz, respirable cristobalite, respirable SiC particles, and SiC fibers, for each year of employment in the SiC industry. Information on employment outside the SiC industry was not available. Individual cumulative exposure was summed up over all years of exposure. Cumulative exposure to each of the six exposure factors was categorized in three *a priori* defined groups (low, medium, and high) by tertiles of person-years of follow-up.

Table 1. Mean years of employment with standard deviation (SD), and geometric mean (GM) geometric standard deviation (GSD), and estimated arithmetic mean (AM) of intensity of exposure to specific exposure factors, by department and period of employment, for 1687 male long-term Norwegian silicon carbide industry workers employed 1913-2003.

		Employment before 1960				Employment after 1959		
		GM	GSD	AM†		GM	GSD	AM†
Furnace department (n)*	232				584			
Years of exposure (mean / SD)	7.2 (6.4)				9.5 (7.3)			
Total dust (mg/m^3)		9.3	3.1	18		3.8	3.1	7.1
Respirable dust (mg/m^3)		1.1	2.5	1.6		0.55	2.5	0.84
Respirable quartz (mg/m^3)		0.015	3.4	0.033		0.0045	3.5	0.0096
Respirable cristobalite (mg/m^3)		0.014	6.3	0.074		0.0022	4.6	0.0072
Respirable SiC (mg/m^3)		0.12	4.8	0.41		0.064	5.4	0.27
Fibers (fibers/cm^3)		0.33	3.1	0.62		0.20	2.6	0.31
Processing department (n)*	166				537			
Years of exposure (mean / SD)	9.4 (8.3)				9.5 (7.3)			
Total dust (mg/m^3)		12	2.1	16		5.2	2.2	7.2
Respirable dust (mg/m^3)		1.0	2.3	1.4		0.60	2.2	0.82
Respirable quartz (mg/m^3)		0.0056	2.3	0.0078		0.0032	2.2	0.0044
Respirable cristobalite (mg/m^3)		0.0075	2.3	0.011		0.0019	2.2	0.0026
Respirable SiC (mg/m^3)		0.67	2.9	1.2		0.34	2.7	0.55
Fibers (fibers/cm^3)		0.057	2.5	0.088		0.030	2.5	0.047
Maintenance department (n)*	187				453			
Years of exposure (mean / SD)	9.6 (9.1)				10.3 (7.8)			
Total dust (mg/m^3)		5.6	1.9	6.9		3.5	2.1	4.7
Respirable dust (mg/m^3)		0.55	1.8	0.65		0.52	2.1	0.68
Respirable quartz (mg/m^3)		0.0039	1.8	0.0046		0.0035	2.1	0.0047
Respirable cristobalite (mg/m^3)		0.0038	1.8	0.0046		0.0018	2.1	0.0023
Respirable SiC (mg/m^3)		0.17	1.9	0.20		0.12	2.0	0.15
Fibers (fibers/cm^3)		0.19	1.9	0.23		0.10	2.4	0.14
Other, low exposed (n)*	88				276			
Years of exposure (mean / SD)	12.3 (10.7)				11.6 (8.7)			
Total dust (mg/m^3)		0.22	3.8	0.53		0.11	3.5	0.24
Respirable dust (mg/m^3)		0.021	3.7	0.048		0.015	3.4	0.031
Respirable quartz (mg/m^3)		0.00020	3.7	0.00047		0.00011	3.4	0.00023
Respirable cristobalite (mg/m^3)		0.00025	3.8	0.00062		0.00047	3.6	0.0011
Respirable SiC (mg/m^3)		0.0077	3.7	0.018		0.0050	3.3	0.010
Fibers (fibers/cm^3)		0.0072	3.4	0.015		0.0044	3.3	0.0088

* n: Number of workers. The sum of n is more than 1687, as each person may have been employed in several departments, and in both periods.

† AM: Arithmetic mean, estimated from geometric mean and geometric standard deviation, as described by Seixas et al.[13].

Each job code was assigned a department affiliation; "Furnace department", including mixing of raw materials, furnace process, and removal of non-reacted and partly reacted material; "Processing department", including refining of the SiC into the specific grain sizes; "Maintenance department", including mechanics, electricians, and other maintenance personnel serving all departments; and "Other, low exposed personnel", including laboratory workers, stock-house workers, and office workers. Persons with employment in more than one department, or with unknown affiliation, were allocated to a "Mixed employment" group. To this "Mixed employment" group the furnace department contributed 2,863 years of exposure, the processing department 2,692 years of exposure, the maintenance department 2,171 years, and the group of "Other, low exposed" jobs 1,343 years of exposure.

Statistical analyses

Standardized incidence ratios (SIR) were calculated as the ratio between observed and expected numbers of lung cancer cases. Expected numbers were based on the national cancer incidence rates for men, summed up in 5-year age and period groups. We performed SIR analyses of lung cancer stratified by department and by category of cumulative exposure to all exposure factors except asbestos, where a dichotomous exposure indicator was used. In order to account for the induction and latency time of lung cancer development, we also included analyses with 10 and 20 years lagging of exposure[14]. We calculated 95% confidence intervals for each risk estimate, assuming a Poisson distribution of the observed cases. Poisson regression analyses were performed for comparison of lung cancer risks between departments, using the "Other, low exposed" category as the reference group. These analyses were adjusted for age (< 55 / 55-74 / ≥ 75 years) only; for age and smoking (ever-, never-, unknown); and were also performed among ever-smokers only. Exposure-response

associations were studied using Poisson regression analyses of lung cancer related to categories of exposure, adjusted for age, among ever-smokers. Adjustment for period of diagnosis was not included in the final models, as inclusion of this variable did not change the estimates. Tests of trend were done by fitting a Poisson regression model for the linear effect of the exposure variables, assuming a constant increase in the log rate ratio per exposure category level[15]. These analyses were also done with 10 and 20 years lagging of exposure. As an alternative to exposure lagging, Jahr's model[16] (modified by Checkoway[14]) using time-weighted cumulative exposure, was also applied. This model has been proposed for studying exposure-response associations with agents that are retained in active forms in the target tissues[14], and it was applied on quartz, cristobalite, and fiber exposure, with and without a clearance factor assuming 10 years half-life of the investigated exposure factors.

The relative importance of the specific exposure factors cristobalite, SiC, and SiC fibers was studied by constructing Poisson regression models including two or more exposure variables at a time. In order to limit the number of variables in the models, and to increase the stability of the analyses, we here used continuous exposure variables, which were justified by the monotonous increasing risk ratios of the categorized variables. Cumulative exposure to each exposure factor was log-transformed, due to skewed distribution of the exposure. Correlation between exposure factors was investigated using Pearson's correlation coefficient ($r_{Pearson}$) between log-transformed cumulative exposures. Correlations between the cumulative exposure factors were moderately high ($r_{Pearson}$ 0.51-0.77), except the correlation between quartz and cristobalite ($r_{Pearson}$ 0.84), justifying analyses with SiC particles and fibres, and one of the crystalline silicas (cristobalite) simultaneously in the model. The relative effects of exposure factors were evaluated by studying how the effect estimate of one factor changed

when a second factor was included in the model, and whether inclusion of a second factor contributed to a better fit of the model, according to the likelihood ratio test. These analyses were done among ever-smokers only. All p-values are two-sided.

All statistical analyses were performed using Stata 11 (StataCorp LP, College Station, TX, USA).

RESULTS

The lung cancer risk in this cohort of long-term SiC workers was increased compared to the general male population (SIR 1.6, 95% CI: 1.3, 2.1, 62 cases) (table 2). The risk was highest among workers in the furnace department (SIR 2.3), and among those with employment from more than one department (SIR 1.9) (table 2). Corresponding results were seen in the internal analyses, using the "Other, low exposed" category as reference group.

Table 2. Observed number of cases (Obs), standardized incidence ratio (SIR) and incidence rate ratio (IRR) with 95% confidence intervals (CI) of lung cancer among 1687 male Norwegian long-term silicon carbide industry workers employed 1913-2003 and followed up 1953-2008, adjusted for age and smoking.

Department	n	Person-years	Obs	SIR	95% CI	IRR*	95% CI	IRR†	95% CI	IRR‡	95% CI
All	1687	42910	62	1.6	1.3 to 2.1						
Other, low exp	175	5082	3	0.6	0.2 to 1.9	1.0		1.0		1.0	
Furnace	387	9405	20	2.3	1.5 to 3.5	3.8	1.1 to 12.8	2.6	0.8 to 8.7	2.5	0.7 to 8.4
Processing	347	7867	9	1.4	0.7 to 2.7	2.1	0.6 to 7.6	1.6	0.4 to 5.9	1.3	0.3 to 4.9
Maintenance	313	8043	9	1.4	0.7 to 2.6	2.0	0.5 to 7.4	1.5	0.4 to 5.7	1.4	0.4 to 5.4
Mixed	465	12512	21	1.9	1.3 to 2.9	2.8	0.8 to 9.4	2.2	0.7 to 7.5	2.1	0.6 to 7.1

* Adjusted for age (0-54/55-74/≥75 years)

† Adjusted for age (0-54/55-74/≥75 years) and smoking (ever-/never-smokers and unknown)

‡ Ever-smokers only (n=1166), adjusted for age (0-54/55-74/≥75 years)

SIR analyses stratified by categories of cumulative exposure factors showed significantly increased risks with highest level of all the four specific exposure factors (table 3). The risk estimate in the highest category of cumulative exposure to all exposure factors increased when exposure was lagged 20 years. Internal analyses among ever-smokers, using the same cumulative exposure categories, gave an increasing risk with increasing exposure to all exposure factors, and a statistical significant test of trend for cristobalite and total dust (table 4).

Table 3. Observed number of cases (Obs) and standardized incidence ratio (SIR), with 95% confidence intervals (CI) of lung cancer among 1687 long-term Norwegian silicon carbide (SiC) industry workers employed 1913-2003 and followed up 1953-2008, by categories of cumulative exposure, and with exposure lagging 0 and 20 years.

	No lag					20 years lag of exposure				
Cumulative exposure	N	Person-years	Obs	SIR	95% CI	N	Person-years	Obs	SIR	95% CI
Total dust										
0-30 mgxyears/m^3	1101	14349	9	0.9	0.5 to 1.7	1615	32343	23	1.1	0.8 to 1.7
30-87 mgxyears/m^3	1001	14188	15	1.4	0.9 to 2.4	675	5700	13	1.5	0.9 to 2.6
87-900 mgxyears/m^3	671	14374	38	2.2	1.6 to 3.1	351	4867	26	3.0	2.0 to 4.4
Respirable dust										
0-3.8 mgxyears/m^3	1156	14186	9	0.9	0.4 to 1.7	1623	33047	25	1.2	0.8 to 1.8
3.8-10 mgxyears/m^3	1066	14082	20	1.8	1.2 to 2.8	651	5495	16	1.9	1.2 to 3.1
10-87 mgxyears/m^3	701	14642	33	2.0	1.4 to 2.9	342	4367	21	2.6	1.7 to 3.9
Quartz										
0-0.026 mgxyears/m^3	1096	14286	11	1.1	0.6 to 1.9	1619	32564	29	1.4	1.0 to 2.0
0.026-0.077 mgxyears/m^3	998	14169	20	1.8	1.1 to 2.7	653	5447	15	1.8	1.1 to 3.0
0.077-2.3 mgxyears/m^3	668	14455	31	1.9	1.4 to 2.7	344	4899	18	2.0	1.3 to 3.3
Cristobalite										
0-0.028 mgxyears/m^3	1030	14083	10	1.0	0.5 to 1.8	1616	32592	25	1.2	0.8 to 1.8
0.028-0.093 mgxyears/m^3	902	14346	17	1.4	0.9 to 2.3	645	5344	17	2.0	1.2 to 3.2
0.093-2.7 mgxyears/m^3	673	14480	35	2.3	1.6 to 3.2	351	4974	20	2.4	1.5 to 3.7
SiC										
0-0.83 mgxyears/m^3	970	14111	14	1.3	0.7 to 2.1	1616	32293	27	1.3	0.9 to 1.9
0.83-3.0 mgxyears/m^3	941	14096	14	1.3	0.8 to 2.2	677	5865	14	1.6	0.9 to 2.7
3.0-60 mgxyears/m^3	697	14703	34	2.2	1.6 to 3.1	357	4752	21	2.6	1.7 to 3.9
Fibers										
0-0.50 fibersxyears/cm^3	925	13788	13	1.2	0.7 to 2.1	1619	31648	24	1.2	0.8 to 1.8
0.50-2.0 fibersxyears/cm^3	1018	14897	15	1.3	0.8 to 2.2	682	6466	14	1.6	0.9 to 2.6
2.0-93 fibersxyears/cm^3	614	14225	34	2.2	1.6 to 3.0	336	4796	24	2.6	1.8 to 3.9

Table 4. Incidence rate ratios (IRR) and 95% confidence intervals (CI) for lung cancer among 1166 ever-smoking Norwegian long-term silicon carbide (SiC) industry workers employed 1913-2003 and followed up 1953-2008, by categories of cumulative exposure, and with exposure lagging 0 and 20 years.

	No lag			20 year lag of exposure		
	IRR*	95% CI	p_{trend}	IRR*	95% CI	p_{trend}
Total dust						
0-30 mgxyears/m^3	1.0			1.0		
30-87 mgxyears/m^3	1.0	0.4 to 2.4		1.4	0.7 to 3.0	
87-900 mgxyears/m^3	1.9	0.9 to 4.0	p=0.04	3.0	1.6 to 5.6	p=0.001
Respirable dust						
0-3.8 mgxyears/m^3	1.0			1.0		
3.8-10 mgxyears/m^3	1.7	0.7 to 4.0		1.6	0.8 to 3.2	
10-87 mgxyears/m^3	2.0	0.9 to 4.4	p=0.09	2.4	1.3 to 4.6	p=0.007
Quartz						
0-0.026 mgxyears/m^3	1.0			1.0		
0.026-0.077 mgxyears/m^3	1.3	0.6 to 2.8		1.5	0.8 to 2.9	
0.077-2.3 mgxyears/m^3	1.5	0.7 to 3.1	p=0.3	1.5	0.8 to 2.8	p=0.2
Cristobalite						
0-0.028 mgxyears/m^3	1.0			1.0		
0.028-0.093 mgxyears/m^3	1.2	0.5 to 2.7		2.0	1.0 to 3.9	
0.093-2.7 mgxyears/m^3	2.0	0.9 to 4.1	p=0.04	2.2	1.1 to 4.1	p=0.02
SiC						
0-0.83 mgxyears/m^3	1.0			1.0		
0.83-3.0 mgxyears/m^3	0.7	0.3 to 1.5		1.0	0.5 to 2.1	
3.0-60 mgxyears/m^3	1.4	0.7 to 2.6	p=0.2	2.2	1.2 to 4.1	p=0.02
Fibers						
0-0.50 fibersxyears/cm^3	1.0			1.0		
0.50-2.0 fibersxyears/cm^3	1.0	0.5 to 2.2		1.4	0.7 to 2.9	
2.0-93 fibersxyears/cm^3	1.7	0.8 to 3.3	p=0.1	2.3	1.2 to 4.4	p=0.009

* Adjusted for age (0-54/55-74/≥75)

Lagging of exposure with 20 years gave significant tests of trend for all exposure factors except quartz (table 4). With 10 years lag of exposure the results did not differ from the non-lagged analyses (not shown in table). The indicator of exposure to asbestos showed no association to lung cancer incidence (not shown in table). The "Jahr" model with time-weighing of exposure did not give increasing risk estimates with increasing exposure levels (not shown in table). When a clearance factor assuming 10 year's half-life was added to the model[14], an exposure-response association was seen with cristobalite exposure, but no significant test of trend (not shown in table).

In Poisson regression models using log-transformed cumulative exposure, the effect estimates of the other exposure factors were substantially reduced when cristobalite was added to the model (table 5). Adding cristobalite to a model already including SiC gave a significant likelihood ratio test, indicating a stronger effect from cristobalite. The effect estimate of cristobalite, on the other side, was somewhat reduced, and no longer significant when fiber was included in the model. Adding fibers in a model already including SiC reduced the effect estimate of SiC and gave a significant likelihood ratio test, but somewhat weaker than cristobalite. Quartz was not included in this model because of the high correlation with cristobalite ($r_{Pearson}$=0.84) introducing collinearity. With quartz in the model the effect estimates of both cristobalite and fiber increased considerably, whereas the effect estimate of quartz was reduced to about 0.5, indicating that the effect of both fiber and cristobalite was stronger that the effect of quartz.

Table 5. Incidence rate ratios (IRR) and 95% confidence intervals (CI) for lung cancer related to log-transformed cumulative exposure to cristobalite, SiC fibers, and SiC particles, among 1166 male ever-smoking Norwegian long-term silicon carbide industry workers employed 1913-2003 and followed up 1953-2008, adjusted for age and the other exposure factors.

	Smokers, N= 1166, 30714 PYR, 58 cases			
	IRR	95% CI	LR-test*	$r_{Pearson}$†
Cristobalite	1.9	1.2 to 2.9		
Cristobalite with SiC	2.0	1.2 to 3.3	p=0.8	0.74
with fibres and SiC	1.6	0.8 to 3.3	p=0.8	
Cristobalite with fibres	1.5	0.8 to 2.9	p=0.4	0.76
with SiC and fibres	1.6	0.8 to 3.3	p=0.4	
Fiber	1.9	1.2 to 2.9		
Fibres with SiC	1.7	1.1 to 2.9	p=0.6	0.5
with SiC and cristobalite	1.3	0.7 to 2.6	p=0.2	
Fibres with cristobalite	1.3	0.7 to 2.6	p=0.2	0.76
with cristobalite and SiC	1.3	0.7 to 2.6	p=0.8	
SiC	1.4	1.0 to 2.1		
SiC with fibres	1.1	0.7 to 1.8	p=0.03	0.5
with fibres and cristobalite	0.9	0.5 to 1.6	p=0.2	
SiC with cristobalite	0.9	0.5 to 1.6	p=0.02	0.74
with cristobalite and fibres	0.9	0.5 to 1.6	p=0.4	

* LR-test: Likelihood ratio test comparing the actual model with the model containing one less exposure factor

† $r_{Pearson}$: Pearson's correlation coefficient

DISCUSSION

We have, in this cohort of SiC workers, documented a 2-3 times increased risk of lung cancer associated with the highest level of cumulative exposure to all the investigated exposure factors. When two or more exposure factors were included in a Poisson model, lung cancer risk was most strongly associated with cristobalite exposure. An association with exposure to SiC fibers was also demonstrated, but this association was less marked than the cristobalite association. Exposure to quartz and SiC dust seemed to be of less importance.

Crystalline silica is classified as carcinogenic to humans (Group 1) by IARC 1997[4]. According to McDonald & Cherry[17], the excess risk of lung cancer associated with crystalline silica exposure was shown primarily in manufacturing industries, with high temperature processes as a common feature. Cristobalite is a high temperature crystalline silica polymorph. *In vivo* studies have shown that cristobalite produces a more rapidly developing pulmonary fibrosis[18, 19], and is cleared less effectively from the airways[20] than quartz. Cristobalite exposure, however, is relatively infrequent in epidemiological studies, as cristobalite is a result of quartz heating, and thus limited to special industries. Some of the epidemiologic studies giving the strongest evidence for an association between crystalline silica exposure and lung cancer are studies from the diatomaceous earth industry, where cristobalite is the most abundant crystalline silica polymorph[21]. The highest exposed workers in our study had cumulative respirable cristobalite exposure estimates of 0.093-2.7 mg x years/m^3, whereas the mean intensity of respirable cristobalite exposure in the furnace hall before 1960 was estimated to have been 0.074 mg/m^3. Very few other studies have reported the levels of exposure to cristobalite. Rafnsson et al. reported respirable cristobalite exposure levels of 0.03-0.7 mg/m^3 in the Icelandic diatomaceous earth industry, but did not

report cumulative exposure levels[22]. Rice et al. reported mean cumulative levels of 2.2 mg x years/m^3 respirable crystalline silica, (maximum cumulative level 63 mg x years/m^3) in the diatomaceous earth industry[23]. Compared to these two studies, the historical cristobalite exposure levels estimated in our study was relatively low. Due to high correlation between cristobalite and quartz estimates, it was not possible in this study to separate the effect of quartz from the effect of cristobalite. However, it seems clear that cristobalite was the stronger factor of the two.

Since silicon carbide fibers (whiskers) were introduced as strengthening material in ceramics, several *in vivo* and *in vitro* studies have been performed in order to determine the toxicological importance of these fibers. This interest was amplified after SiC fibers were discovered as part of the working atmosphere in the furnace hall of the SiC producing industry[9]. So far, studies have shown that SiC fibers have similarities with asbestos fibers, both with respect to direct cell toxicity[5, 24], and with respect to biopersistence[25]. The results of the previous Norwegian SiC lung cancer study indicated that there could be an exposure-response association with SiC fibers, but the exposure data were too sparse to draw any firm conclusions[3]. In the exposure assessment study which forms the basis of the JEM, SiC fibers were measured in parallel with total dust, giving job group specific estimates of SiC fiber exposure relative to total dust exposure [11]. Although fibers had a stronger association with lung cancer than quartz and SiC, this effect was somewhat reduced when cristobalite was included in the multivariate model. However, the effect estimate (IRR) of SiC fibers after inclusion of cristobalite and SiC particles in a multivariate model was still 1.3, and we cannot from this study exclude an effect of SiC fiber exposure on lung cancer incidence.

The exposure assessment study does not take into account the use of personal protective equipment (PPE), due to limited information about historical use of respirators. Such information was available only for 16% of the measurements before 2002. In the 2002/2003 investigation 26% of the workers reported no use of PPE and 61% used PPE some of the time[11]. Plant personnel were interviewed on historical use of PPE, and they informed that the use was infrequent in earlier years, and that the compliance is better now. Not adjusting for the use of respirators might thus lead to an overestimation of the inhaled dose, especially for the recent years. This again might lead to an underestimation of the exposure-response relation in the epidemiological analyses, but as all the lung cancer cases had their first employment before 1981, this underestimation is assumed to be minor.

The information about smoking habits in the present study is limited to ever-/never-smokers and unknown. In order to adjust for the well known effect of smoking on lung cancer risk, we chose to perform the more advanced analyses on the sub-cohort of ever-smokers. By using the sub-cohort of ever-smokers in the IRR-analyses at department level we got approximately the same risk estimates as when we adjusted for smoking. The advantage of limiting the analyses to ever-smokers was to obtain a better balance in the data, with less risk of collapse of the analyses due to few cases in some of the groups. A high correlation between intensity of smoking and degree of dust exposure could still give a possible bias, but this question could not be addressed with the information available in this study.

Potential exposure to other carcinogenic agents, such as asbestos and PAHs, should also be considered. We had in this study only qualitative information about asbestos exposure, based on the plant personnel's knowledge about asbestos use in earlier times[12]. Using an indicator of ever-exposure to asbestos, we found no evidence for an association with lung cancer incidence. The fact that the incidence of mesothelioma was at the level of the general population[2], also indicates that asbestos exposure has not been of great relevance in this industry. Only a few measurements of PAHs have been performed in the Norwegian SiC industry, and the main part of these show low exposure levels, except in measurements related to crane operators prior to the introduction of fresh air ventilated crane cabins. Only one of the lung cancer cases in our study worked as a crane operator in this period. The mean of other measurements in the furnace hall was 1.0 $\mu g/m^3$, compared to the Norwegian occupational exposure limit of 40 $\mu g/m^3$. This, in addition to the fact that other cancers associated with PAH exposure, such as bladder cancer, was not increased in the SiC industry[2], indicate that other factors than PAH were the more important carcinogenic agents.

As lung cancer develops slowly, with 10-20 years induction and latency time, exposure lagging is frequently used in order to weight the assumed etiologically most important exposures most heavily[14]. Lagging of exposure with 10 and 20 years implies that each person-year of follow-up is assigned a cumulative level of exposure corresponding to the cumulative level 10 or 20 years earlier. The 10 years lagging gave no other results than the non-lagged analyses, whereas with 20 years lagging of exposure more significant exposure-response associations were seen, indicating a longer induction and latency period than 10 years. In order to study the effect of slow clearance of deposited particles and fibers from the lung, we also applied a model of time-weighted exposure. In this “Jahr” model, exposures are

weighted relative to the number of years since exposure. These analyses did not show any exposure-response associations, in contrast to the analyses with 20 years lag. The results are difficult to interpret, but we might speculate that the "Jahr" model gives an overcorrection for the time factor in this context. The model was originally applied for latency consideration related to silicosis, and its relevance to carcinogenesis remains unclear.

CONCLUSION

We have found a 2-3 times increased risk of lung cancer associated with the highest level of cumulative exposure to quartz, cristobalite, SiC particles, and SiC fibers among workers in the Norwegian SiC industry. Multivariate models indicated that cristobalite was the most important occupational risk factor, but exposure to SiC fibers also appeared to contribute to the increased lung cancer risk. Exposure to quartz and SiC particles was not seen to influence the lung cancer incidence.

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